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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

DECEMBER, 1956

ORIGINAL ARTICLES

PRELIMINARY REPORT ON THE EFFECTS OF A PLASMA LIPID MOBILIZING FACTOR IN MAN*

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Seifter and Baeder[2] recently reported the isolation from man and several animal species of a plasma fraction which has potent lipid mobilizing effects. A single intravenous or intramuscular injection into animals of this plasma dialysate was followed by a marked hyperlipemia. Repeated injections produced a striking depletion of fat depots and weight loss despite hyperphagia. Because of these observations and their evident potential significance, studies were undertaken to determine the effects in man following injection of this naturally occurring plasma fraction. Our initial observations form the basis of this report.

Methods and Materials. The material which contained the lipid mobilizing factor (LMF) used in this study was a water-clear, sterile liquid dialysate of horse plasma. The term LMF used here refers to the dialysate which contains the active factor although these terms are not synonymous. Since the yield of this naturally occurring factor from plasma is increased roughly one thousandfold by treatment of the animal with large doses of cortisone, the horses were injected with 5 mg. per kg. of cortisone prior to blood collection. After separation of the plasma, it was dia-

*Presented at the 48th Annual Meeting of the American Society for Clinical Investigation, Atlantic City, April 30, 1956.

lyzed through viscose casing against demineralized and pyrogen-free water at 25° C. for 72 hours. The dialysate was concentrated at 75° C. and 0.2 mm. Hg pressure, and the concentrated material was then freeze-dried. The final sterile, pyrogen-free product contained 30 mg. of dried dialysate per ml.

Of the initial patients selected, five had metastatic carcinoma, one had a cerebral vascular accident associated with thrombocytopenic purpura, and one patient was in the terminal stage of leukemia. Although the dialysate is protein-free, skin tests of the material which had been diluted to 1:10 with sterile normal saline were made routinely prior to injection in the first 12 patients. No positive wheal and flare reactions were encountered. The LD_{50} of this material (lot No. 2)* was 60 mg. per kg. in animals, but a dosage range of from 0.25 to 1.0 mg. per kg. was found to be effective in these patients.

Initially, a single intravenous injection of LMF in a dosage range from 0.25 to 1.0 mg. per kg. was made into the human subjects. Measurements of pulse rate, respiratory rate, and blood pressure were made at close intervals prior to, during, and following injection for a period of 3 hours. Measurements of blood lipids, glucose, and eosinophils were made on control and periodic post-injection venous blood samples. Lipid phosphorus was determined by the method of Fiske and SubbaRow[1], total fatty acids by the method of Stoddard and Drury[5], and total cholesterol by the Schoenheimer-Sperry technique[2]. The rate of blood clotting before and after injection was studied by the Lee-White and 6 tube silicone techniques. All patients were maintained in a fasting state during this part of the study in order to eliminate postprandial hyperlipemia. Later, daily intravenous injections into the same patient of 1.0 mg. per kg. of LMF were made over a period from 5 to 14 days without dietary restriction. In one patient who received daily injections of LMF for 14 consecutive days, daily measurements of the body weight, daily basal metabolic rates, weekly thyroid I_{131} uptake studies, and weekly complete blood counts were performed. In this patient measurements of a properdin-like material also were performed prior to, during, and after the experimental period.

Results. The results of injection may be considered to fall within two groups. The first group consists of 25 patients who received a single intravenous dose of LMF. The results of a single injection on the blood lipids for the first 12 of these patients are shown in Table 1. The average lipid values of this group before and after injections are shown in Fig. 1. These data show that the fatty acid, total cholesterol, and lipid phosphorus values are approximately doubled after a single injection of LMF. Maximum values are reached 2 to 3 hours after injection and remain elevated for at least 24 hours. An illustrative case is shown in Fig. 2. The remaining 13 patients in this group had a similar elevation of their plasma lipids. One patient, however, showed no response to 1.0 mg. of LMF per kg. but did experience a threefold rise of plasma lipid values following injection of 3.0 mg. of LMF per kg.

In addition to the lipid levels, temperature, pulse, respiration, and blood pressure, blood glucose, total eosinophil counts, and coagulation times by the Lee-White and silicone techniques were determined. During a 4-hour period there were no significant changes from the control values of these determinations.

One patient (C.L.) in this group was a 40-year-old white male who had coronary artery insufficiency as manifested by previous myocardial infarctions and angina pectoris. Although the injection of 1.0 mg. per kg. of LMF resulted in a marked rise of plasma lipids, there were no changes in serial electrocardiograms, and the patient did not experience angina pectoris during a 4-hour period.

One patient (J.S.) of this group died 11½ hours following injection of 1.0 mg. per kg. of LMF. The patient was critically ill from an acute exacerbation of myeloblastic leukemia at the time of injection. Death was not attributed to

*Studies now in progress on lot No. 3 indicate that the LD_{50} in rats is greater than 250 mg. per kg. intravenously.

TABLE 1.—EFFECT OF A SINGLE INJECTION OF LMF ON PLASMA LIPIDS IN 12 PATIENTS

	Weight in kg.	*Dose mg./kg.*	*Time in hours*	*Total Cholesterol mg./100 ml.*	*Total Fatty Acid mg./100 ml.*	*Lipid Phosphorus mg./100 ml.*
			0	126	282	6.85
CASE No. 1			½	238	341	10.07
M.W., aged 65, white female.	64	0.25	1	275	354	10.37
Generalized carcinomatosis			2	244	358	10.59
			3	238	367	9.18
			0	132	275	7.00
CASE No. 2			½	263	392	10.52
S.Q., aged 74, white male.	70	0.50	1	290	411	10.98
Metastatic carcinoma			2	285	400	11.20
of rectum			3	276	398	10.90
			0	186	295	7.2
CASE No. 3			½	288	392	10.55
J.S., aged 57, Negro male.	60	1.0	1	310	404	11.69
Metastatic carcinoma			2	309	399	11.88
of stomach			3	326	408	11.42
CASE No. 4						
J.S., aged 48, white female.	52	1.0	0	122	202	4.28
Acute myelogenous leukemia			½	650	440	14.07
			0	172	301	6.8
CASE No. 5			½	322	486	11.28
S.M., aged 55, white male.	78	1.0	1	344	480	11.67
CVA with thrombocytopenic			2	388	492	11.80
purpura			3	298	490	11.25
			0	210	325	6.9
CASE No. 6			½	395	512	11.55
L.B., aged 64, Negro male.	70	1.0	1	412	492	11.91
Metastatic carcinoma			2	404	488	12.24
of rectum			3	400	486	12.02
			0	218	305	7.28
CASE No. 7			½	375	440	11.65
B.S., aged 56, white female.	42.5	1.0	1	404	482	11.68
Pemphigus			2	429	495	12.42
			3	430	512	12.85
			4	435	518	12.69
			0	226	312	7.94
CASE No. 8			½	342	486	10.42
A.N., aged 18, white female.	41	1.0	1	418	502	12.68
Scleroderma			2	508	586	15.48
			3	526	592	16.48
CASE No. 9	Approx.		0	218	292	6.72
M.V., aged 81, white female.	45	1.0	1	350	412	12.48
Cerebral arteriosclerosis			3	368	485	12.26
			0	300	324	8.29
CASE No. 10			1	499	584	14.65
C.L., aged 48, white male.	60	1.0	2	584	650	18.20
Coronary artery disease			3	576	670	17.42
			0	235	318	6.24
CASE No. 11			2	482	526	12.28
E.H., aged 25, Negro female.	40	1.0	6	312	442	11.68
Rheumatoid arthritis			24	322	402	10.95
			0	302	329	7.0
CASE No. 12			2	486	502	11.24
M.T., aged 53, Negro female.	65	1.0	6	520	586	12.86
Rheumatoid arthritis			24	418	492	10.41

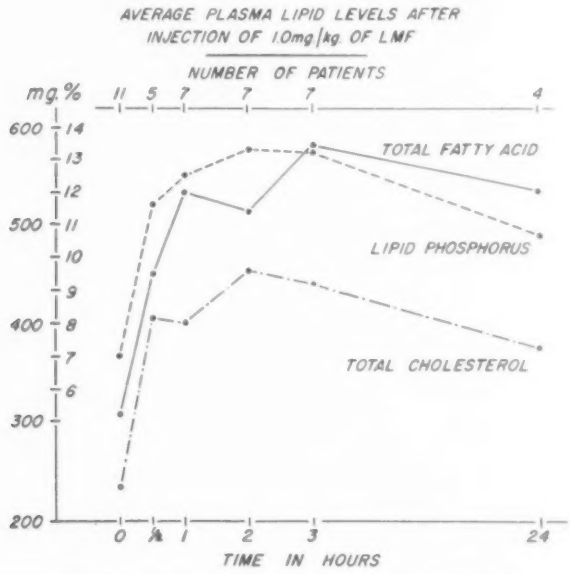

Fig. 1.—The average fasting plasma lipid levels are shown before and after a single injection of 1.0 mg. per kg. of LMF. The number of patients in each time group is indicated on the top of the graph.

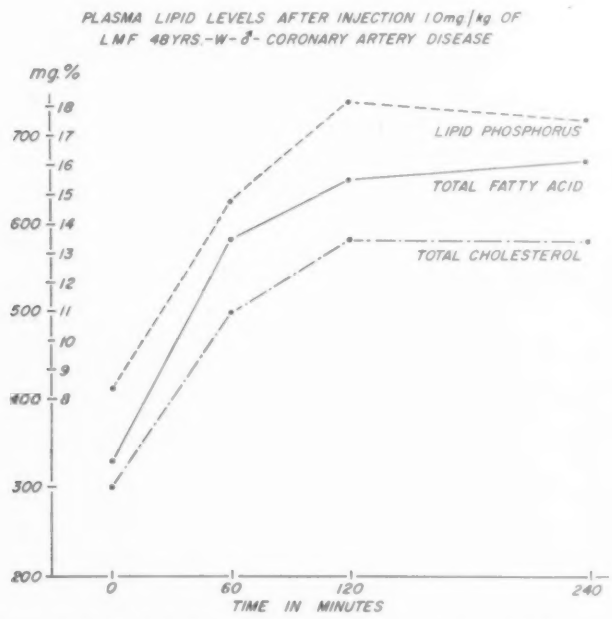

Fig. 2.—The plasma lipid levels before and after a single injection of 1.0 mg. per kg. in patient C.L. are shown. The patient was in a fasting state during the procedure.

any effect of LMF. There was a marked rise in plasma lipids (total cholesterol rose from 122 mg. to 650 mg. per 100 ml.) in the single post-injection specimen obtained. It is of interest to note that this patient had been treated with 150 mg. of cortisone daily for several months prior to death.

injection on the eighth day when his total cholesterol was 960 mg. per 100 ml., total fatty acid 1,058 mg. per 100 ml. and the lipid phosphorus was 19.55 mg. per 100 ml. Also shown in Table 2 are the lipid values 5 days after daily injections of LMF were discontinued when the plasma concentrations remained elevated 2 to 3 times above the controls.

TABLE 2.—EFFECT OF DAILY INJECTIONS OF LMF ON PLASMA LIPIDS IN PATIENT J.H., A 39-YEAR-OLD WHITE MALE WITH MODERATE INTERNAL HYDROCEPHALUS AND PARTIAL RIGHT HEMIPLEGIA

Day of Treatment	*Time of Specimen*	*Total Cholesterol mg./100 ml.*	*Total Fatty Acid mg./100 ml.*	*Lipid Phosphorus mg./100 ml.*
	Control before injection	240	352	7.92
1	1 hr. after injection	418	872	12.65
	3 hrs. after injection	512	940	14.62
2	Before injection	362	758	10.84
3	Before injection	495	806	11.62
6	Before injection	542	900	12.84
7	1 hr. after injection	872	1002	18.69
8	2 hrs. after injection	906	1058	19.55
9	Before injection	524	796	10.86
10	Before injection	562	824	11.92
13	Before injection	672	842	13.85
14	6 hrs. after injection	854	986	14.65
5 days after injections discontinued		675	882	12.65
33 days after injections discontinued		164	258	6.2

TABLE 3.—EFFECT OF DAILY INJECTIONS OF LMF ON PLASMA LIPIDS IN PATIENT P.F., A 71-YEAR-OLD NEGRO MALE WITH CEREBRAL INFARCTION

Day of Treatment	*Time of Specimen*	*Total Cholesterol mg./100 ml.*	*Total Fatty Acid mg./100 ml.*	*Lipid Phosphorus mg./100 ml.*
0	Control	286	320	6.28
1	Control before injection	262	312	5.96
	3 hrs. after injection	502	666	13.28
2	Before injection	396	484	10.42
5	Before injection	418	408	9.22
6	Before injection	462	413	8.72

The second group consisted of 2 patients who received daily LMF injections for 14 and 5 days respectively. Tables 2 and 3 show the striking elevation of plasma lipids in these 2 subjects. The first of these patients, J.H., received LMF for 14 consecutive days. His rising fasting lipid values are shown in Fig. 3. The highest plasma concentrations obtained during the course of this study were obtained 2 hours after

No evidence of cumulative toxicity occurred in this patient. Measurements of the 24-hour I_{131} uptake by the thyroid were made during the control period and at weekly intervals thereafter. Complete blood counts, total eosinophil counts, and coagulation times were performed at the same intervals. None of these determinations was af-

fected. No significant change was noted in the level of a properdin-like substance° which was measured before, during, and 5 days after completion of the 14-day series of injections. Daily determinations of basal metabolic rate were obtained on 12 days and showed no significant variation from the control values. The BMR which was done before and one hour after injection likewise showed no change.

The second patient (P.F.) who received LMF for 5 consecutive days was a 71-year-old Negro male admitted with a flaccid right hemiplegia and aphasia. He died 13 days after admission to the hospital and 30 hours after receiving the last of 5 daily injections of LMF. Death was not attributed to any LMF effect or toxicity. Gross necropsy findings consisted primarily of marked atherosclerosis of the left middle cerebral artery and a large area of left cerebral encephalomalacia.

A total of 48 intravenous injections of LMF have been given to 28 patients. The single consistent finding following injection has been a marked elevation of the plasma lipids.

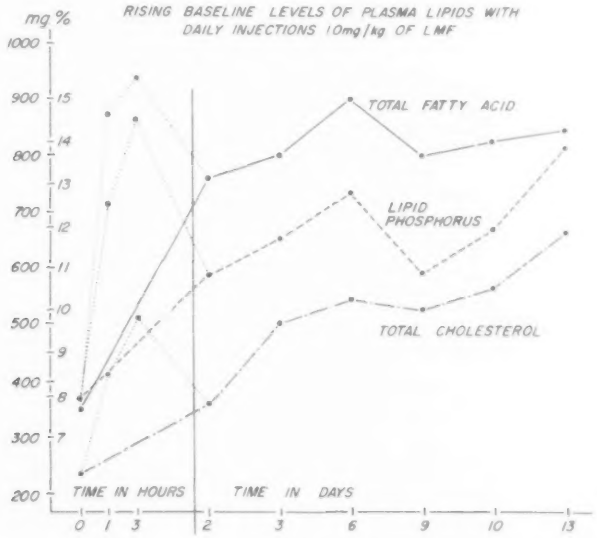

Fig. 3.—The effect on the fasting plasma lipid levels of 14 daily injections of 1.0 mg. per kg. of LMF in patient J.H., a 48-year-old white male, is shown. The fasting lipid levels 1 and 3 hours after a single injection are indicated by the dotted curve on the left of the graph. The levels also remained elevated 5 days after the injections were discontinued.

Discussion. The single striking result of the administration of the plasma dialysate which contains LMF has been the consistent and marked elevation of plasma lipids of all chemical classes, namely, cholesterol, fatty acids, and phospholipids. With the doses employed in this study, the elevation persisted for at least 24 hours following a single injection, and was present 5 days after daily injections were dis-

°Kindly performed by Dr. Kenneth M. Schreck who found that the administration of LMF did not change the hemolytic activity of unheated serum for tannic acid treated human erythrocytes (type O Rh negative).

continued in one patient (J. H.). Since the plasma of many of the patients becomes visually lipemic, there also may be an alteration in the physical state of the lipids and lipoprotein moieties. Further studies of the physical properties of the lipids, utilizing ultracentrifugal and electrophoretic techniques, are anticipated.

The source of the elevated plasma lipids in animals has been demonstrated to be the usual perirenal, omental, subcutaneous, and mesenteric fat depots. The weight loss and depletion of fat depots in animals after high doses of LMF would appear to indicate the fats undergo catabolism, or excretion, or both, rather than mere transport and redeposition. The livers and spleens of these animals did not reveal lipidosis on histologic examination. In this connection, studies to determine the fate of the elevated plasma lipids induced by the injection of LMF are currently under way. The human subject who received LMF for 14 days in this study had no changes in his BMR, thyroid I_{131} uptake, or body weight. It should be noted that the dose administered to him was considerably smaller than that given the dogs which exhibited hyperphagia and weight loss[3]. Fat and nitrogen balance studies in man, including determinations of the respiratory quotient, are planned.

Although hyperlipemia has been reported to increase blood coagulation, our preliminary studies in these patients have shown no significant changes in coagulation times by the Lee-White or silicone methods. In this connection, it has been noted that the LMF induced hyperlipemia and plasma lactescence in animals was not altered by anticoagulant doses of heparin[3].

Although the exact identification of LMF has not yet been made,* it has been clearly demonstrated by Seifter and Baeder that LMF is not cortisone or a related steroid. Moreover, LMF activity could not be demonstrated in the plasma of hypophysectomized rats even after cortisone administration. However, the injection of LMF to such hypophysectomized rats was followed by a hyperlipemic response.

It will be a future concern to delineate the role of the effects of LMF in states of altered fat metabolism, hypercholesterolemia, xanthomatous diseases, nephrosis, and similar diseases. It is interesting to speculate upon the possible role of LMF in atherosclerosis. Whether the high plasma lipids give rise to additional deposition of lipid in arterial coats, or whether the administration of LMF will mobilize lipids from atheromata as from fat depots. is currently under study in animals. Seifter, Baeder and Ziliken[4] have found that the administration of LMF to rabbits on a standard Anitschkow diet did not aggravate the experimental atheromatous lesions, and LMF given to rabbits on a fat-free diet did not initiate such lesions.

It is clear that much further investigation of the role and effects of LMF are indicated and anticipated. However, the studies reported herein confirm in man the potent lipemia-producing effects of LMF demonstrated recently in animals.

Summary. Preliminary studies of the effects in man of a plasma dialysate, which contains a naturally occurring lipid mobilizing factor (LMF) were undertaken. A single intravenous injection of this material in 25 patients, who were maintained in a fasting state, was followed by a marked rise in the plasma total cholesterol, total fatty acids, and lipid phosphorus. No significant change was noted in blood glucose, total eosinophil counts, or coagulation times.

*Since this manuscript was prepared, LMF has been crystallized, and it appears to be a heat stable peptide (Seifter, Baeder and Ziliken[4]).

Serial electrocardiograms and the degree of angina pectoris were unaffected in a patient with coronary artery disease. Striking hyperlipemia was also induced in patients who received LMF daily for 5 and 14 days. Daily determinations of BMR, and weekly determinations of I_{131} uptake, complete blood counts, coagulation times, and a properdin-like substance were unchanged. Two deaths which occurred during these studies were not attributed to any toxic effects of LMF. The potential significance of LMF is discussed and attention is directed to some of the areas in which future investigation of LMF may be rewarding.

ACKNOWLEDGMENTS: The technical assistance of William Beckmann, J. Dachiw, J. Howitz, M. Klenk, and E. E. Livingston, Jr. is gratefully acknowledged.

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SUMMARIO IN INTERLINGUA

Reporto Preliminari Super le Effectos de un Factor de Mobilisation de Lipido Plasmatic in Humanos

Studios preliminari del effectos in humanos de un dialysato de plasma, que contine un naturalmente occurrente factor de mobilisation de lipido (FML), ha essite executate. Un sol injection intravenose de iste material in 25 patientes, qui esseva mantenite in stato jejun, esseva sequite per un marcate augmento del total cholesterol de plasma, del total acidos grasse, e del phosphoro de lipido. Nulle significative alteration esseva notate in glucosa sanguinee, in total numerationes de eosinophilos, o in tempores de coagulation. Electrocardiogrammas in serie e le grado de angina de pectore non esseva afficite in un patiente con morbo de arteria coronari. Frappante grados de hyperlipemia esseva etiam inducite in patientes qui recipeva FML in administrationes diurne durante 5 e 14 dies. Determinationes diurne del metabolismo basal e determinationes septimanal del acception de I^{131}, complete numerationes sanguinee, tempores de coagulation, e un substantia properdin-oide non esseva alterate. Duo mortes que occurreva in le curso de iste studios non esseva attribuite a ulle effecto toxic de FML. Le signification potential de FML es discutite. Es signalate certe areas in que futur investigationes de FML pote esser profitabile.

EFFECTS OF FAT INGESTION AND HEPARIN ADMINISTRATION ON SERUM LIPIDS OF "NORMAL", HYPERCHOLESTEROLEMIC, HYPERLIPEMIC AND ATHEROSCLEROTIC SUBJECTS*

By Peter T. Kuo, M.D.**

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AND

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(From The Edward B. Robinette Foundation, Medical Clinic and the Chemistry Section, William Pepper Laboratory, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania)

Atherosclerotic cardiovascular disease, leading to death in early life from coronary occlusion, has been observed in a significant number of patients having essential familial hypercholesterolemia (Alvard[2], Barr, Rothbard and Eder[4], Bloom, Kaufman and Stears[7], Cook *et al.*[8], Lever, Smith and Hurley[16], and Rigdon and Willeford[21]). A close association between idiopathic hyperlipemia and the premature development of clinical atherosclerosis has also been reported (Lever *et al.*[16] and Soffer and Murray[24]). More recently, it was learned by us that postprandial lipemia can precipitate anginal pain in patients with severe coronary artery disease and, moreover, that intravenous injection of heparin can promptly relieve this type of anginal pain (Kuo and Joyner[14,15]). Consequently, it seemed to us worthwhile to make a comparative study of: (*Experiment A*) the serum lipids of "normal," hypercholesterolemic, hyperlipemic, and atherosclerotic subjects, in the fasting state and following intravenous injection of heparin; (*Experiment B*) the serum lipids of these same groups of subjects during the postabsorptive period and following heparin injected at the height of their postprandial lipemias.

Methods. Subjects. 1) *"Normal"* were 5 males and 5 females, from 16 to 39 years of age, laboratory technicians, medical students and physicians, all in good health. 2) *Hypercholesterolemic* consisted of 12 patients having total serum cholesterol above 350 mg. per 100 ml. Six of these 12 had familial hypercholesterolemia and xanthoma tendinosum, and 2 of the 6 had also xanthelasma of the eyelids. In age they ranged from 6 to 52 years. 3) *Hyperlipemic* were 7 patients with lactescent plasma and serum total esterified fatty acids of 20 mEq./L. or higher in the fasting state. They ranged from 32 to 48 years in age. Three of the 7 had cutaneous xanthomatous plaques and papules. 4) The *atherosclerotic* consisted of 15 patients, from 42 to 61 years of age, having clinical manifestation of either coronary or peripheral arterial disease or both.

During the initial study (*Experiment A*) venous blood for lipid determinations was taken from each subject, in the fasting state and again 15 to 20 minutes after the intravenous injection of 10 to 25 mg. of heparin. In the subsequent study (*Experiment B*) each subject was given a fatty meal of heavy cream (40% butter fat by weight) flavored

*This study has been supported in part by grants from the Life Insurance Research Fund, American Heart Association, and Eli Lilly and Co. Presented in part at the Annual Meeting of the American Society for the Study of Arteriosclerosis, Chicago, Illinois, November 7, 1955.

**This work was done during the tenure of a Research Fellowship of the American Heart Association.

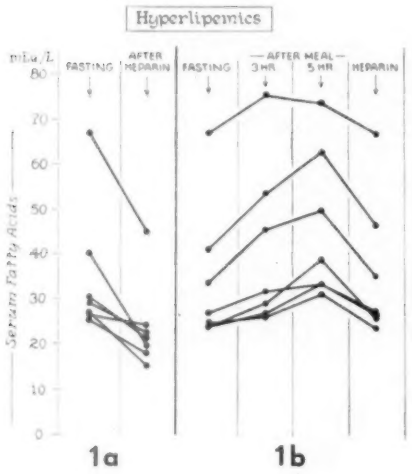
with cocoa and sweetened with cyclamate, a standardized amount of 0.6 gm. per pound of body weight. Samples of venous blood were taken during fasting, 3 to 5 hours postprandially, and 15 to 20 minutes after intravenous injection of 10 to 25 mg. of heparin either 3 or 5 hours after fat consumption. In order to minimize and standardize the progressive *in vitro* clearing of the postheparin blood sample, plasma lactescence determination, paper electrophoresis of the serum, and estimation of serum total esterified fatty acids were made within one hour after this blood was drawn.

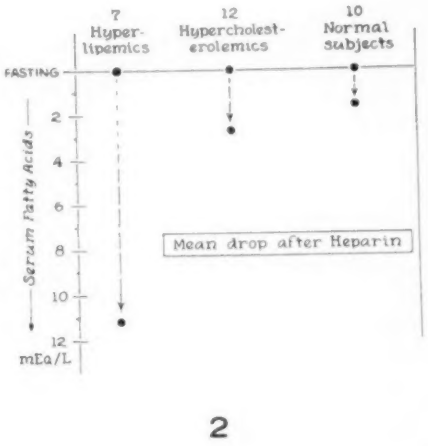
The methods used for serum lipid analyses were as follows: for serum cholesterol that of Abell, Levy, Brodie and Kendall[1]; for serum phospholipid, that of Zilversmit and Davis[29]; and for serum total esterified fatty acids, a modified method of Stern and Shapiro[25]. The turbidity of the plasma was determined by means of a Coleman Junior spectrophotometer. A red filter (650 mu) was used for all readings. Paper electrophoresis of serum was performed according to the technique of Grossmann and Hannig[10], as modified by van Frijtag Drabbe and Reinhold[27]. A tenth of a milliliter of serum was regularly used for each lipid analysis. The paired and simultaneously run strips were stained for lipids with Sudan Black B, (Swahn[26]), and for proteins with amido black 10 B. The lipid pattern was plotted from readings obtained by scanning of the unclarified stained paper strips with a photovolt densitometer. The lipid strips were read with an orange filter (640 mu). By attending to the details of the technique, consistent reduplication of the serum lipid pattern can be obtained from several simultaneously run electrophoretic strips on the same blood specimen.

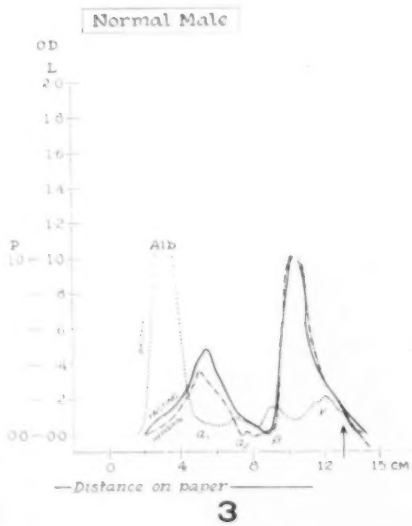
Results. SERUM LIPIDS IN THE FASTING STATE (EXPERIMENT A). The serum of all 7 patients with *hyperlipemia* in the fasting state showed a marked elevation of the total esterified fatty acid. In 5 of the 7 patients, serum cholesterol and phospholipids were also elevated. Their total serum cholesterol values varied from 224 to 724 mg., with an average of 439 mg. per 100 ml. (range of our normal subjects being 155 to 288 mg. per 100 ml.). Their serum phospholipids varied from 198 to 655 mg., averaging 447 mg. per 100 ml. (range of our normal subjects being 170 to 290 mg. per 100 ml.) Their serum total esterified fatty acids ranged from 24.2 to 67.2 mEq./L., averaging 34.0 mEq./L. (normal being 6.8 to 12.0 mEq./L.). Intravenous injection of 10 to 25 mg. of heparin to these hyperlipemic patients caused a prompt decrease of the fasting serum total esterfied fatty acid level, ranging from 2.3 to 20.5 mEq./L. Figure 1*a* illustrates the changes observed in serum total esterified fatty acids in the 7 hyperlipemic patients following heparin injection. The magnitude of the change appears to be roughly dependent upon the level of the esterified fatty acids in the blood, being most marked in 2 patients who had very high levels and relatively small in the remaining 5 patients who had moderate elevations.

The serum of 12 *hypercholesterolemic* patients in the fasting state showed a considerable elevation of cholesterol (ranging from 372 to 802 mg., averaging 506 mg. per 100 ml.); and a slight to moderate elevation of phospholipids (ranging from 338 to 675 mg., averaging 408 mg. per 100 ml.) and total esterified fatty acids (ranging from 11.0 to 19.5 mEq./L., averaging 15.6 mEq./L.). A small fall in the total serum esterified fatty acids concentration, ranging from 1.3 to 4.2 mEq./L., was observed in this group of patients following heparin injection.

Figure 2 shows the mean drop of fasting total serum esterified fatty acids in three groups of subjects: *hyperlipemic* a mean decrease of 11.7; *hypercholesterolemic* of 2.3, and "*normal*" of 1.7 mEq./L. No significant change in total serum cholesterol and phospholipid levels was observed in any of these subjects following heparin injection. Hence, the lowering of the total serum esterified fatty acid levels by heparin was essentially a reflection of







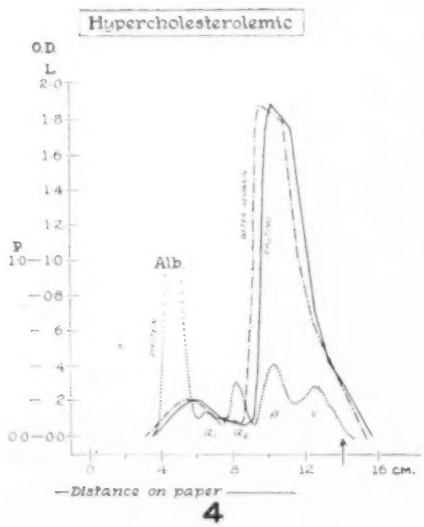


Fig. 1*a*.—Serum total esterified fatty acid values of each of the 7 hyperlipemic patients in the fasting state and 20 minutes after the intravenous injection of 10 to 25 mg. of heparin.

Fig. 1*b*.—Serum total esterified fatty acid curve of each of the 7 hyperlipemic patients over a period of 5 hours following fat ingestion, and 20 minutes after heparin injection at the height of postabsorptive lipemia.

Fig. 2.—Average fall of the fasting serum total esterified fatty acid levels of the 7 hyperlipemic and 12 hypercholesterolemic patients, and 10 normal subjects 20 minutes after the intravenous injection of 10 to 25 mg. of heparin.

Fig. 3.—Serum electrophoretograms of a 26-year-old male resident physician. Optical density of the lipid and protein strips is plotted against the distance from the line of application of the sera to the paper (indicated by arrow). Fasting and 20 minutes postheparin serum lipid curves; and serum protein curves are shown.

Fig. 4.—Fasting, and postheparin serum lipid and protein electrophoretograms of a 6-year-old boy with essential familial hypercholesterolemia.

changes in the triglyceride content of the sera.

Three of the 15 patients with coronary or peripheral arterial disease, or both, had mild hyperlipemia and 5 had hypercholesterolemia. The serum lipid levels of the remaining 7 patients were considered to be within normal limits. The responses of these *atherosclerotic* patients to heparin varied between that of the normal subjects, and of the hypercholesterolemic and hyperlipemic subjects.

The electrophoretic lipoprotein pattern of a healthy "*normal*" 26-year-old man (H.G.) is shown in Fig. 3. Although the beta lipid zone is considerably larger than the alpha zone, the beta zone is relatively narrow and low. In 2 of the 5 normal female subjects, the alpha and beta lipid zones are about equal in size and height. Fasting serum lipid patterns of 8 of the 10 normal subjects were not significantly affected heparin. This is illustrated in Fig. 3.

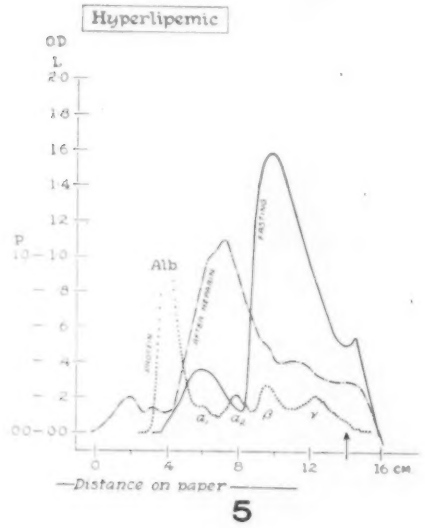
Figure 4 shows the fasting and postheparin electrophoretic patterns of a 6-year-old boy (R.K.) with essential familial *hypercholesterolemia*. His total serum cholesterol ranged from 1,100 to 1,400 mg. per 100 ml. before he was put on a low fat diet. Subsequently his total serum cholesterol level varied between 650 and 802 mg. per 100 ml. In comparison with the lipid pattern of a normal person, his alpha lipid zone is very small, and the beta lipid zone is marked by increase in height with some increase in width. Heparin injection caused a slight increase of the electrophoretic mobility of the lipid zones, but the respective sizes of the alpha and beta zones showed very little change.

Figure 5 is an example of the serum lipid electrophoretic patterns in patients with *hyperlipemia*. The fasting and postheparin serum lipid patterns were obtained from a 42-year-old man (M.R.) with arteriosclerotic occlusive disease of the terminal aorta. After heparin his fasting serum total esterified fatty acids level fell from 40.4 to 19.6 mEq./L. Like the hypercholesterolemic patients, his fasting lipid curve shows a relatively small alpha zone and a much exaggerated beta zone However, the increase in width of the beta zone is the most prominent feature. In addition, a large neutral fat zone appeared behind the beta lipid zone, extending for some distance backward beyond the line of application. After heparin, all the lipid zones decreased in area. The alpha zone migrated to a point ahead of the serum albumin, and the beta zone moved to a region between alpha$_1$ globulin and serum albumin.

In general, the degree of turbidity of the plasma has been found to be roughly proportional to its total esterified fatty acid content. Exceptions were seen in patients with very high serum cholesterol values, where the plasma lactescence readings may be normal or only slightly increased, despite a moderately large increase of their serum total esterified fatty acid content.

SERUM LIPIDS FOLLOWING FAT INGESTION (EXPERIMENT B). Most of the changes in blood lipids that followed heparin administration were closely related to the triglyceride content. Therefore, the effect of fat ingestion and heparin administration at the height of postprandial lipemia was studied in all of our subjects.

Figure 1*b* is a graph of the serum total esterified fatty acid levels of the 7 *hyperlipemic* patients in the fasting state, 3 and 5 hours after ingestion of a standard fatty meal and 15 to 20 minutes after intravenous heparin given 5 hours postprandially. In all but one patient the serum lipid curve



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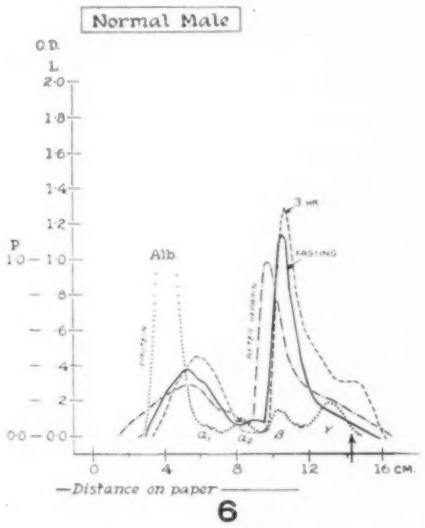

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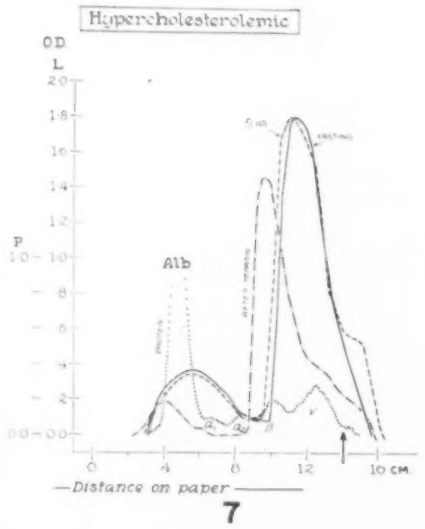

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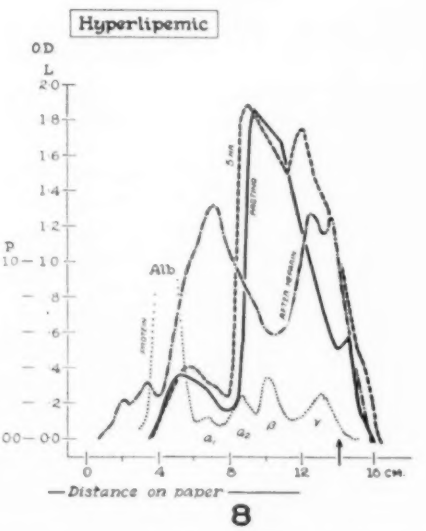

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Fig. 5.—Fasting, and postheparin serum lipid and protein electrophoretograms of a 42-year-old male patient with idiopathic hyperlipemia.

Fig. 6.—Serum lipid and protein electrophoretograms of the healthy young male physician presented in Fig. 3. Serum lipid curves obtained during the fasting state, 3 hours after fatty meal and 20 minutes after heparin given at the height of postabsorptive lipemia are correlated with the serum protein curve.

Fig. 7.—Fasting, 5 hour postprandial, and postheparin (given 5 hours after fat ingestion) serum lipid curves of a 45-year-old male hypercholesterolemic patient are shown in correlation with the serum protein curve.

Fig. 8.—Fasting, 5 hour postprandial and postheparin (given 5 hours after test meal) serum lipid curves of the hyperlipemic patient presented in Fig. 5.

shows a progressive rise in the serum fatty acid level, due to an increase in triglyceride up to 5 hours postprandially; in the one exception, the fatty acid level shows a slight, probably insignificant drop 5 hours after the test meal. The 5-hour postabsorptive serum total esterified fatty acid curves of 10 of the 12 *hypercholesterolemic*, 10 of the 15 *atherosclerotic*, and 2 of the 10 *normal* subjects are similar to those seen in the patients with idiopathic hyperlipemia. Heparin administration at the height of the postabsorptive lipemia resulted in variable but consistent lowering the serum triglyceride level of all the subjects.

Serum phospholipid levels of most of the subjects showed a slight tendency to rise during the postprandial period; while serum cholesterol levels were unaffected by fat ingestion. No significant change in either the serum cholesterol or the phospholipid content was observed in any of the subjects following heparin injected near the peak of postprandial lipemia.

The fasting, 3-hour postprandial, and postheparin serum lipid patterns of the *normal* male (H.G.) are shown in Fig. 6. By comparison with the fasting curve, the beta lipid zone in the 3-hour postprandial curve is widened toward the line of application, where a small neutral fat zone is seen. Heparin injected at this time caused a lowering of all the lipid zones and an increase in their rates of migration in the anodal direction. These changes, though less dramatic, are similar to those occurring in patients with idiopathic hyperlipemia.

Figure 7 indicates that near the peak of postprandial lipemia, 5 hours after fat ingestion, the beta lipoprotein zone of a 45-year-old male *hypercholesterolemic patient* shows a further increase in width. The neutral fat zone located behind it is also quite prominent. Heparin injected 5 hours postprandially resulted in a considerable decrease in the size of the various lipoprotein zones. Again, the electrophoretic mobility of all the lipid zones is increased.

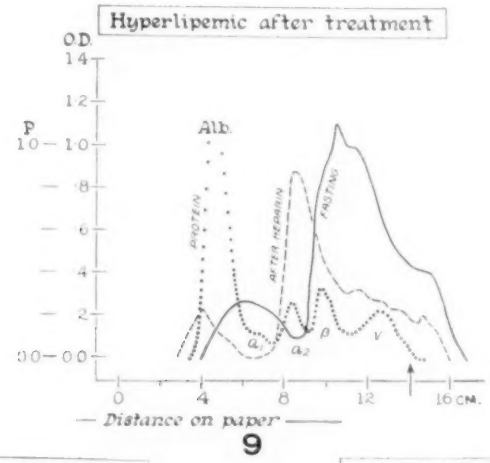
Fat ingestion and heparin administration produced the bizarre serum lipid patterns in Fig. 8 in a patient with idiopathic *hyperlipemia*. Five hours after a fatty meal, the broad and tall beta lipoprotein zone of this patient became even broader than that of the fasting curve, through the encroachment of a very large neutral fat zone behind it. The beta lipoprotein zone can be seen to extend into the alpha$_2$ globulin region. The lipid curve after heparin injection shows a marked lowering of the lipid peaks and also a great increase in their anodal migration, with a diffuse spreading of lipids on the filter paper.

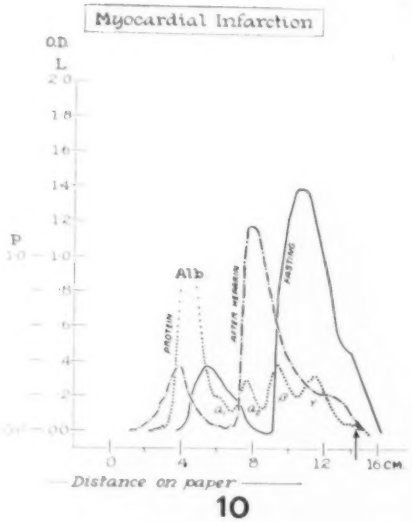
In contrast to the picture presented in Fig. 5, Fig. 9 shows the lipid patterns of the same patient 8 months after he was put on a 20 gm. fat per day diet and 30 gm. of sitosterol per day. In the fasting state, his beta lipoprotein and neutral fat zones have become much smaller in size and their changes following intravenous heparin have become much less marked than those prior to therapy. His serum esterified fatty acid level has fallen from 40.4 to 17.8 mEq./L., and his serum cholesterol and phospholipids are now within normal limits.

Electrophoretic study in the fasting state of 7 of the 15 *atherosclerotic* patients with normal or borderline normal serum lipid values have a relatively broad beta lipoprotein zone. Both the alpha and beta lipoprotein zones show a variable increase in electrophoretic mobility and a decrease in area following heparin. Figure 10 is an example. The lipid curves were obtained from a 53-year-old female patient (H.L.) with

hypertension, old myocardial infarction, and frequent angina pectoris. Only two of the 10 "*normal*" subjects in the fasting state showed similar changes in the electrophoretic patterns following heparin injection.

Figure 11 shows the fasting, 3 and 5 hour post-prandial serum lipid curves of a 54-year-old female patient (H. S.) with severe coronary artery disease and angina pectoris. Plasma lactescence measurement showed more than 25%





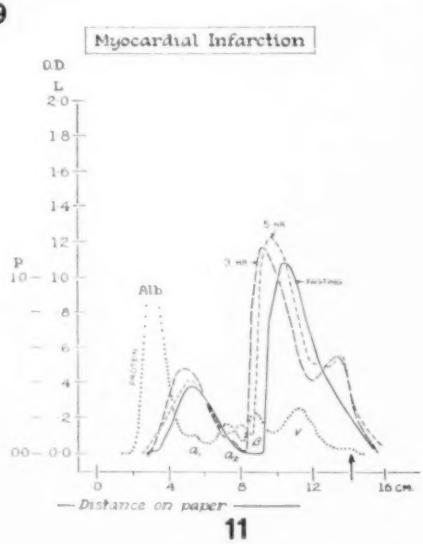


Fig. 9.—Fasting and postheparin serum lipid curves of the hyperlipemic patient presented in Figs. 5 and 8, 8 months after treatment.

Fig. 10.—Fasting, and postheparin serum lipid and protein electrophoretograms of a 53-year-old female patient with hypertension and myocardial infarction.

Fig. 11.—Fasting, 3 and 5-hour postprandial serum lipid curves of a 54-year-old female patient with myocardial infarction and angina pectoris.

clearing of the turbidity 5 hours postprandially, as compared with the 3-hour sample. It is apparent that despite clearing, the 5-hour lipid curve is in most respects quite similar to the 3-hour curve. Little or no heparin-like activity is demonstrable by the electrophoretic method in blood samples taken during the period of "physiological clearing" in any of our subjects.

Discussion. The possibility of utilizing either fat feeding alone or in conjunction with intravenous heparin injection in order to bring out certain distinctive features in the blood lipid patterns of atherosclerotic subjects has been explored by a number of investigators (Block, Barker and Mann[6], Moreton[18], Nikkila[19], Schwartz, Woldow and Dunsmore[23], and Woldow, Chapman and Evans[28]). Our studies here reported indicate, by the blood chemistry figures and the electrophoretic results, that heparin administration or fat ingestion, or both, induces certain acute alterations in the serum lipids. The extent of the changes in a given individual is probably governed by a number of complex factors; nevertheless the most important factor is the level of the abnormal lipids present in the plasma. Significant changes in the serum lipids were observed following heparin injection or fat feeding or both in almost all the patients with hyperlipemia and hypercholesterolemia. These changes were small or insignificant in our "normal" subjects who showed little or no abnormal elevation of their serum lipid values.

In the fasting state, 2 of our 10 normal subjects, both of whom, however, had a family history of coronary disease, and all of our 7 patients with clinical atherosclerosis who had normal serum lipid values showed a relatively broad serum beta lipid zone in the electrophoretic pattern. The changes in their serum lipids following heparin administration were very similar to those ensuing upon heparin in a hyperlipemic patient. This strongly suggests that a mild hyperlipemic state is probably present in a certain number of atherosclerotic patients and also in a small number of "normal" subjects. Thus, a heparin test given during the fasting state appears to have value in detecting individuals with low fat tolerance having an impaired ability to metabolize neutral fat and other lipids. The value of this test in the study of patients with subclinical atherosclerosis remains to be established.

Although limitations of the quantitative measurement of the various lipoprotein fractions according to the intensity of staining on paper electrophoretogram (Jenks and Durrum[13]) do not warrant precise interpretation, several distinctive features were observed in the electrophoretic distribution of the serum lipids in each group studied. Densitometry of the stained serum lipid fractions showed a sharp increase in height and some increase in width of the beta lipid zone in patients with hypercholesterolemia, and it showed a marked widening of the beta zone and some increase in height in patients with hyperlipemia, as compared with normal subjects. The alpha lipid zone was small in both the hypercholesterolemic and hyperlipemic groups. Since a greater proportion of atherosclerotic patients have been shown to have certain degrees of hypercholesterolemia or hyperlipemia or both, it is to be expected that these patients would tend to have an increase in the concentration of beta lipoprotein and a decrease in the concentration of alpha lipoprotein (Barr, Russ and Howard[5], Nikkila[19], and Rosenberg, Young and Proger[22]). On the other hand, a number of atherosclerotic patients with normal serum lipid values usually do not

show a decrease in the alpha lipid zone in their electrophoretograms.

In the study of the electrophoretic mobility of the various serum lipid fractions, it is essential that electrophoresis be performed within 1 to 2 hours after the blood sample is drawn from the patient, as electrophoretic mobility of serum lipoproteins increases on aging of the blood sample, with or without refrigeration (Herbst and Hurley[11], Moore *et al.*[17] and Oncley and Gurd[20]). Having avoided such artefacts as are caused by excessive fat hydrolysis *in vitro*, we consistently observed a slight to moderate increase in anodic mobility of the beta lipid zone in patients with hyperlipemia; this appears to be principally related to a displacement phenomenon due to an excessive "piling up" of triglyceride particles in and about the beta lipid zone. However, the possibility that metabolic breakdown products of neutral fat present in the beta lipoproteins (Anfinsen[3]) may also play a part in this electrophoretic change must be considered.

In normal subjects in the fasting state, little or no increase in the electrophoretic mobility of the lipoproteins resulted from intravenous heparin injection. Postprandially, however, heparin injection produced a marked increase in the mobility of both the alpha and beta lipid fractions in normal subjects, as in idiopathic hyperlipemic patients. These observations confirm those of Gordon[9], and of Herbst and his associates[12] that heparin injection releases free fatty acids from the neutral fat molecules, and that the binding of the fatty acids to alpha and beta lipoproteins results in an increase of their electrophoretic mobility. The associated decrease in the height of the various lipid zones following heparin injection is, we believe, probably due to the diffuse spreading of lipid material on filter paper and does not represent an actual decrease in the concentration of the serum lipids.

Nikkila and others[19] found an increase in the amount of alpha lipoproteins in alimentary hyperlipemia following heparin injection, and it has been postulated that heparin causes a transformation of the low density lipoproteins (beta) to higher density lipoproteins (alpha). However, in the present study we failed in any of our subjects to demonstrate an increase in the size of the alpha lipid zone electrophoretically after heparin injection. Moreover, comparative studies of the pre- and post-heparin lipid curves obtained from hyperlipemic patients clearly indicates that heparin merely caused the beta lipoproteins to migrate with the speed of the alpha lipoproteins and that the alpha zone is made to migrate with a speed faster than serum albumin. Thus, our data agree with those of Herbst and associates[12] as to lack of evidence to support the concept that heparin causes a transformation of beta lipoproteins to alpha lipoproteins.

Failure to demonstrate a significant increase in electrophoretic mobility of the serum lipoproteins with "physiological clearing" of the alimentary hyperlipemia might indicate that little or no heparin-like substance is involved in fat metabolism. A more plausible explanation, however, is that the slow excretion of minute quantities of heparin-like substance *in vivo* during the postprandial period does not suddenly release an excessive amount of free fatty acids to produce a measurable effect upon the electrophoretic properties of the serum lipoproteins.

Summary. 1. The effects of fat ingestion and heparin administration upon serum lipids were investigated in 10 normal subjects, 12 hypercholestero-

lemic, 7 hyperlipemic, and 15 atherosclerotic patients.

2. In paper electrophoresis the serum beta lipid zone of hypercholesterolemic patients showed a sharp increase in height and some increase in width. In patients with hyperlipemia, this lipid zone became very broad and the increase in height was less. In both groups of patients the alpha lipid zone was consistently small.

3. Eight out of 15 of our atherosclerotic patients were found also to have hypercholesterolemia or hyperlipemia or both. Of the 7 who had normal blood chemistry levels, the electrophoretic patterns were relatively normal.

4. Heparin given in 10- to 25-mg. doses intravenously in the fasting state caused little or no change in the serum lipid levels and electrophoretic patterns in normal and hypercholesterolemic subjects, but produced sharp changes in the hyperlipemic patients.

5. Seven atherosclerotic patients whose serum lipids were normal or borderline normal in the fasting state showed a slightly broadened beta lipid zone and a moderate increase in electrophoretic mobility of all their serum lipid zones after heparin administration.

6. A varying but progressive increase in the width of the beta lipid zone was observed in all subjects during the postprandial period.

7. Heparin given during the postprandial hyperlipemic state caused a marked increase in the electrophoretic mobility of both the alpha and beta lipid zones in all subjects. The alpha zone moved ahead of serum albumin, and the beta zone migrated with the speed of alpha lipoproteins. No evidence was found to indicate that heparin can cause a transformation of the beta lipoproteins to alpha lipoproteins.

8. No significant increase of heparin-like effect was demonstrable by the electrophoretic method in blood that had undergone "physiologic clearing" several hours after ingestion of a fatty meal.

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SUMMARIO IN INTERLINGUA

Le Effectos del Ingestion de Grassia e del Administration de Heparina Super le Lipidos del Sero de Individuos "Normal," Hypercholesterolemic, Hyperlipemic, e Atherosclerotic

1. Le effectos del ingestion de grassia e del administration de heparina super le lipidos del sero esseva investigate in 10 individuos normal, 12 patientes hypercholesterolemic, 7 patientes hyperlipemic, e 15 patientes atherosclerotic.

2. In electrophorese a papiro le zona de lipidos beta in le sero de patientes hypercholesterolemic monstrava un marcate augmento in altitude e alicun augmento in latitude. In patientes con hyperlipemia iste zona de lipidos deveniva latissime e le augmento in altitude esseva minus. In ambe gruppos de patientes le zona de lipidos alpha esseva regularmente parve.

3. Inter 15 patientes atherosclerotic 8 habeva etiam hypercholesterolemia o hyperlipemia o ambes. Pro le 7 qui habeva nivellos normal de chimismo sanguinee, le configurationes electrophoretic esseva relativemente normal.

4. Heparina administrate intravenosemente in dosages de 10 a 25 mg in le stato jejun causava parve o nulle cambiamento in le nivellos de lipidos del sero o in le configurationes electrophoretic in individuos normal e hypercholesterolemic, sed illo produceva marcate cambiamentos in le patientes hyperlipemic.

5. Septe patientes atherosclerotic cuje lipidos sero esseva normal o quasi normal in le stato jejun monstrava post le administration de heparina un zona de lipidos beta un pauco plus late, e etiam un moderate augmento in le mobilitate electrophoretic de omne lor zonas de lipidos de sero.

6. Un variabile sed progressive augmento in le latitude del zona de lipidos beta esseva observate in omne subjectos durante le periode postprandial.

7. Le administration de heparina durante le stato hyperlipemic postprandial causava un marcate augmento in le mobilitate electrophoretic in omne subjectos de e le zona alpha e le zona beta de lipidos. Le zona alpha avantiava ante le albumina del sero, e le zona beta migrava con le velocitate del lipoproteinas alpha. Il habeva nulle prova que heparina pote causar un transformation de lipoproteinas beta a in lipoproteinas alpha.

8. Nulle augmento significative de un effecto simile a ille de heparina esseva demonstrabile per le methodo electrophoretic in sanguine que esseva subjicite a "depuration physiologic" pro alicun horas post le ingestion de un repasto grasse.

THE EFFICACY OF PENICILLIN V (PHENOXYMETHYLPENICILLIN) IN THE TREATMENT OF MILD AND OF MODERATELY SEVERE PNEUMOCOCCAL PNEUMONIA

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In many respects, the penicillins are ideal antibiotics. They are bactericidal and, though allergenic, they are otherwise almost devoid of toxicity for man. Use of the preparations available previously has been hampered somewhat by their destruction in and irregular absorption from the gastrointestinal tract; and although some have been administered successfully by the oral route, penicillins by mouth have enjoyed limited application. With the advent of penicillin V (phenoxymethylpenicillin) (Welch[6]), a penicillin has become available which is resistant, in large measure, to destruction by gastric secretions and which is absorbed with considerable regularity from the intestinal tract. To test the efficacy of oral penicillin V in the treatment of pneumococcal pneumonia, an infection caused by an organism highly susceptible to its action, has been the purpose of this study.

Method of Study. All patients with evidence of mild to moderately severe acute uncomplicated infection of the lower respiratory tract admitted to the medical wards of the University Division, Kings County Hospital between July 1, 1955, and June 30, 1956, were included initially in the study. Excluded therefrom were seriously and critically ill patients, those with evidence of extrapulmonary pneumococcal disease, and those with pneumonia not of pneumococcal origin.

On admission to the hospital, the following laboratory studies were performed: roentgenogram of the chest, white blood cell count, blood culture and a study of the sputum by direct smear, quellung reaction*, culture and mouse inoculation. The assessment of the severity of illness was based upon the objective historical, physical and laboratory findings listed in Table 1 together with the clinical impression of the hospital physician at the time of his initial examination of the patient.

Because assessment of the usefulness of penicillin V was limited to a study of its efficacy in the treatment of mild and of moderately severe pneumococcal pneumonia and because previous experience had shown the efficacy of intramuscular aqueous penicillin G in such patients to be relatively constant over a period of years, a control group was not included in this study.

Patients treated with penicillin V** received 400,000 units of the drug orally as soon as the clinical diagnosis of pneumonia had been made and 400,000 units at the next 8 o'clock treatment period (A.M. or P.M.). Treatment with 400,000 units orally at 12-hour intervals thereafter was continued

*The capsular typing serum employed was made available through the courtesy of Dr. H. D. Piersma, Lederle Laboratories Division, American Cyanamid Co.

**The penicillin V used in this study was supplied by Wyeth Laboratories, Inc., through the courtesy of Dr. Edward F. Roberts.

until the rectal temperature had been below 99.6° F. for 72 hours.

During the course of illness, the following observations were made: rectal temperature every 4 hours; white blood cell count at intervals of not longer than 3 days; roentgenogram of the chest before discharge or as otherwise indicated and additional cultures of the blood

retain oral medication. Patients in whom the diagnosis could not be substantiated by the isolation of a pneumococcus and by roentgenographic demonstration of pulmonary consolidation were excluded subsequently.

Results. From the data included in the tables, it is evident that penicillin

TABLE 1.—CLINICAL AND LABORATORY DATA IN 73 CASES OF PNEUMOCOCCAL PNEUMONIA

	No.	%
Total Patients:	73	100
Male	57	78.1
Female	16	21.9
White	27	37.0
Negro	46	63.0
Age of Patients:		
Under 40	39	53.4
40–59 years	20	27.4
Over 60	14	19.2
Severity of Disease:		
Mild	48	65.8
Moderate	22	30.1
Severe	3	4.1
Critical	0	0
Duration of Illness Before Admission:		
1 to 2 days	34	46.6
3 to 4 days	21	28.8
5 to 6 days	5	6.8
Over 6 days	9	12.5
Unknown	4	5.5
Indications of Severity:		
Bacteremia	18	24.7
Multilobar involvement	4	5.5
Leukocytes less than 8,000 per c. mm.	7	9.6
Shock	0	0
Disorientation	3	4.1
Alcoholism	12	16.4
Other*	13	17.8
Pneumococcal types:		
I to VIII	53	72.6
Higher types	19	26.0
Untyped	1	1.4
Patients Receiving Prior Treatment:	7	9.6

*Cardiac failure, diabetes, hepatic disease, and others.

of all patients found to have bacteremia at the time of admission.

All patients admitted with a clinical diagnosis of mild or of moderately severe pneumonia were included initially in the study except those with a history of hypersensitivity to penicillin and those unable to take or to

V administered orally in doses of 400,000 units every 12 hours provides a highly effective form of treatment for mild and for moderately severe pneumococcal pneumonia. The speeds of defervescence and of the return of

the leukocyte count to normal were comparable to those following therapy with parenteral penicillin G and in no instance was bacteremia, when present initially, found to persist after 24 hours of treatment with penicillin V.

TABLE 2.—RESULTS OF TREATMENT WITH ORAL PENICILLIN V OF 73 PATIENTS WITH PNEUMOCOCCAL PNEUMONIA

	No.	%
Total Patients:	73	100
Duration of fever following start of therapy:		
1 day or less	17	23.3
2 days	27	37.0
3 days	6	8.2
4 days or more	23	31.5
Duration of WBC greater than 10,000* per c. mm.:		
3 day or less	17	23.3
4 to 6 days	20	27.4
7 days or more	12	16.4
Data not available	11	15.1
Complications:	1	1.4
Deaths:	1	1.4

*Thirteen patients did not have a white blood cell count as high as 10,000 per c. mm. at the time of their hospitalization.

Two therapeutic failures occurred among this group of patients. The first patient was a 26-year-old Negro male admitted on the third day of illness suffering from pneumonia caused by pneumococcus type XII. At the time of hospitalization his temperature was 102° F. and only the basal segment of the right lower lobe was involved. Blood culture was sterile and the leukocyte count was 11,600 per c.mm. The patient was treated with penicillin V according to the protocol. During the next 36 hours his temperature rose and remained in the vicinity of 104° F. and signs of consolidation extended to involve the entire right lower lobe. Accordingly, treatment was changed and the patient was given 300,000 units of aqueous penicillin G intramuscularly every 12 hours. His temperature fell to normal in 32 hours and the patient left the hospital against advice shortly thereafter, forestalling plans to study his ability to absorb orally administered penicillin V.

The second therapeutic failure and only death in this series was that of a 42-year-old colored male chronic alcoholic. He was hospitalized on the first day of illness with uncomplicated lobar pneumonia involving the left lower lobe caused by pneumococcus type XXXIII. On admission, his temperature was 103.2° F., blood pressure 130/70, leukocyte count 7,500 per c.mm. and blood culture sterile. He was treated according to protocol and received one dose of 400,000 units of penicillin V the night of entry. His temperature remained elevated during the next 10 hours at the end of which time the patient got out of bed and fell to the floor. There was no superficial evidence of injury and the patient was returned to bed. He died suddenly an hour later with signs of peripheral vascular collapse. Permission for necropsy was denied.

In this series, complications were rare, a result due in part to the fact that the patients comprising it represent a selected group. Exclusion from the study of seriously and of critically ill patients and of those with a history of sensitivity to penicillin acted doubtless to modify the incidence of complications. One patient, a 42-year-old white male with lobar pneumonia of the right upper lobe caused by pneumococcus type II suffered from delayed resolution and localized fibrosis following treatment with penicillin V and the right upper lobe was resected 2 months after entry into the hospital. The tissue removed showed the histological picture of chronic interstitial pneumonitis. No instance of hypersensitivity to penicillin V was observed.

Because of the few data available today concerning the bacteriology of pneumococcal disease, the incidence of individual pneumococcal types in this series of infections is recorded in Table 3. Noteworthy are the frequency and invasive character of infections caused by pneumococcus type I, the rarity of infection caused by pneumococcus type II and the small proportion of infections caused by pneumococcal types higher than type VIII.

TABLE 3.—DISTRIBUTION OF PNEUMOCOCCAL TYPES IN 73 PATIENTS WITH PNEUMOCOCCAL PNEUMONIA

Pneumococcal Type	*No. of Patients*	*No. with Bacteremia*
I	17	7
II	1	
III	6	1
IV	9	2
V	3	1
VI	2	
VII	9	2
VIII	6	2
IX	2	
XI	1	
XII	4	2
XIV	2	
XVII	1	
XIX	1	
XX	1	
XXII	1	
XXIII	1	
XXVII	1	
XXXIII	4	1
Untyped	1	
Total	73	18

Discussion. From the results of this and of other studies, it would appear that a congener of penicillin highly suitable for oral administration is now available. Indeed, penicillin V seems as satisfactory for administration by mouth as any of the other antibiotic substances considered to be efficacious when given by this route. The convenience afforded both physician and patient and the added comfort for the latter are obvious benefits to be derived from its use.

No attempt has been made in this study to determine the minimally effective dose of penicillin V for the treatment of pneumococcal pneumonia. The amount given and the interval between doses were selected to yield blood levels estimated to be roughly comparable to those achieved by the administration intramuscularly of 300,000 units of aqueous penicillin G every 12 hours. As the studies of Tillet, McCormack and Cambier[4] and of others have shown (Tumulty and Zubrod[5]), this amount of penicillin is quite adequate for the treatment of uncomplicated pneumococcal pneumonia, and the lack of need for bactericidal tissue levels of penicillin throughout the course of treatment has been indicated by the observations of Eagle, Fleischman and Musselman[1] in experimental infections. There is no contraindication other than expense, however, to shortening the interval between treatments to 8 or to 6 hours.

Although none of the patients in this study received parenteral penicillin and although apparent failures of individuals to absorb orally administered penicillin V are infrequent, it would seem advisable, in the routine treatment of pneumococcal pneumonia, that an initial parenteral injection of penicillin G be given to ensure absorption and to lessen delay in the establishment of an effective concentration of drug. Treatment thereafter of mildly and of moderately ill patients with pneumococcal pneumonia with oral penicillin V should prove satisfactory in the majority of instances.

Despite the fact that no hypersensitive reactions to penicillin V were observed in the patients included in this study, their occurrence is to be anticipated. In addition, patients sensitive to other congeners of penicillin may

manifest reactions of hypersensitivity upon initial contact with penicillin V (Peters, Henderson and Prickman[3]). For these reasons, penicillin V should be administered no less discriminatingly than other forms of this valuable group of antibiotics.

Statements concerning the rarity of pneumococcal pneumonia since the advent of antibiotics are heard not infrequently today. Neither the clinical nor bacteriological data accumulated on this medical service over the past 4 years support this impression. At this hospital, pneumococcus is still the cause of most cases of pneumonia and with one exception, the pneumococcal types responsible for the majority of infections in the past preponderate today. The exception is pneumococcus type II which has all but ceased to be a cause of human infection in the Middle Atlantic area in the past decade. Analogous unexplained fluctuations in the incidence of infection caused by this pneumococcal type have been noted in the past (Griffith[2]), and it will not be surprising if the frequency of disease caused by pneumococcus type II increases at some time in the future.

Summary. Orally administered penicillin V in doses of 400,000 units every 12 hours has been used to treat 73 cases of mild and of moderately severe pneumococcal pneumonia. The results indicate that penicillin V is a drug suitable for the treatment of such infections by the oral route.

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SUMMARIO IN INTERLINGUA

Le Efficacia de Penicillina V (Phenoxymethylpenicillina) in le Tractamento de Leve e Moderatemente Sever Casos de Pneumonia Pneumococcal

Administrationes oral de penicillina V in doses de 400.000 unitates omne 12 horas esseva usate in le tractamento de 73 casos de leve e de moderatemente sever pneumonia pneumococcal. Le resultatos indica que penicillina V es un droga appropriate al uso per via oral in le tractamento de tal infectiones.

CLINICAL OBSERVATIONS ON 712 CASES OF TETANUS SUBJECT TO FOUR DIFFERENT METHODS OF TREATMENT: 18.2% MORTALITY RATE UNDER A NEW METHOD OF TREATMENT

By Ricardo Veronesi, M.D.*

In the State of São Paulo, Brazil, tetanus is responsible for 52.6% of the deaths from specific infantile diseases (Galvao[28]), as distinct from those of multiple etiology such as gastroenteritis or bronchopneumonia. Tetanus kills more infants than whooping cough, diphtheria, measles, chickenpox, and anterior poliomyelitis together.

In the Hospital das Clinicas, São Paulo, umbilical tetanus is outstanding among the infectious diseases as a cause of infant mortality (Carvalho *et al.*[13]). From 1944 to 1954, the Hospital admitted 886 cases of tetanus and prior to July, 1955, nonumbilical cases of tetanus accounted for 692 admissions.

During the same 10-year period admissions for other more common diseases were: schistosomiasis, 882 cases; meningitis of all types, 776 cases; chronic or subacute glomerulonephritis, 669 cases; infectious hepatitis, 446 cases; South American blastomycosis, 310 cases; malaria, 249 cases; and typhoid fever, 204 cases.**

The Hospital das Clinicas of the University of São Paulo, with this high incidence, has studied various treatments for tetanus during the past 5 years. Although the patients are treated on several wards, techniques have been standardized and the methods used have reduced tetanus mortality rates to the lowest, thus far reported, of any hospital in the world.

Material for Study. Four groups of patients have been studied since the Hospital das Clinicas opened: The first group of 294 patients, admitted from 1944 to 1949, received the "old" treatment; the second group of 141 patients, admitted from 1950 to 1951, had "mixed" therapy; the third group of 236 patients, admitted from 1952 to 1954, were given "modern" treatment; and, finally, a small group of 21 tetanic patients have undergone hibernation.

In order to evaluate the results obtained in the group undergoing the "modern" treatment, we observed more accurately the 57 cases entering our Clinic during one year and these were examined by Pratt's criteria[45] for the evaluation of a scheme of treatment, that is, according to the seriousness of the cases. This "test group" showed a mortality rate identical to that obtained by other clinics following our standardized treatment.

Cases of umbilical tetanus are not included here because they constitute a separate problem, owing to the peculiar and inherent difficulties of the newborn. Such cases are under an extensive study by Dr. Dacio Pinheiro and the author.

ANALYSIS OF THE MATERIAL OF STUDY. The "test group" consisting of 57 patients on "modern" treatment has been analyzed according to the age groups, the foci, the incubation period, and the "time of onset" which are correlated with mortality (see Tables 1, 2 and 3).

Age apparently influences tetanus mortality, in that the newborn group with umbilical tetanus and the "old age group" (patients over 50 or 60 years of age), had a higher death rate. The former group presents special problems such as difficulty in administering drugs, water and electrolytic control, alimentation, lack of co-operation, inability to expel secretions from upper respiratory tract, the high occurrence of respiratory complications,

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**Data furnished by the Department of Statistics, Hospital das Clinicas, São Paulo, Brazil.

and a low resistance against infections. Such a group, all over the world, has a mortality rate between 70 and 100%.

The suspected focus was located most often in the lower extremities, a natural consequence of their exposure and contact with contaminated objects and soil. The more frequent causes of traumatism of the lower extremities were shoe nails, tools, tin cans, splinters and thorns. There were fewer wounds of the upper extremities and other locations were rarely involved.

Often a suspected focus cannot be found. Such foci, unnoted by the naked eye, can be the source of serious cases of tetanus. Among these are punctures from intramuscular injections, particularly with substances such as calcium salts or quinine which lower the local oxidation-reduction potential. Several cases of serious tetanus occurring after heroin injection in North American addicts (Levinson, Marske and Shein[38]) and have been described recently. Dental foci and small thorn wounds must be considered in the absence of perceptible foci.

TABLE 1.—RELATION BETWEEN AGE GROUPS AND MORTALITY

(Test Group)

Age (years)	*No. of Cases*	*Deaths*	
		Before 48 Hours	*After 48 Hours*
1 to 5	4	1	0
6 to 10	11	1	2
> 10	42	4	4
Total	57	6	6

TABLE 2.—RELATION BETWEEN LOCATION OF FOCUS AND MORTALITY

(Test Group)

Focus	*No. of Cases*	*Deaths*
Lower extremities	43	10
Upper extremities	5	1
Face	1	0
Teeth	1	0
Genitalia	1	0
Gluteal region	1	0
Abdomen	1	0
Not found	4	1
Total	57	12

TABLE 3.—RELATION BETWEEN "ONSET TIME" AND INCUBATION PERIOD TO MORTALITY.

(Test Group)

No. of Cases	*"Onset Time"*	*Inc. Period (days)*	*Mortality (%)*
30	> 48		3.3
25	< 48		44.0
2	Unknown		0
12		1–5	25.0
21		6–10	23.0
16		> 10	18.0
8		Unknown	12.0

The shorter the incubation period, the higher is the mortality, as noted previously (Veronesi *et al.*[54]). A short incubation period accompanies a copious focal production of toxin, which rapidly reaches the central nervous system. Even so, many tetanic patients, after a long period of incubation, are attacked by serious forms of the disease. This is probably due to later contamination of a wound with tetanus bacilli.

In our series, we had the highest incidence of mortality (24%) in those having an incubation period of 10 days or less (33 cases). At the same Hospital, prior to 1947, (Neves and Tranchesi[42]), the mortality rate in a similar group of 66 cases was 42.2%. Vinnard[60] reported a similar group at Louisiana Charity Hospital, New Orleans, with a death rate of 53% (140 cases).

"Onset time" is an expression proposed by Cole[14] to denote the period of time from the first symptoms observed to first spasm. It also is correlated with the mortality rate. Indeed, this time interval is the best sign for prognosis; when longer than 48 hours, the patient has a much better chance of surviving. According to Cole[14], an "onset time" of less than 48 hours indicates roughly that one or more minimal lethal doses have already reached the central nervous system; the survival time may be roughly estimated as three times the "onset time."

With regard to the value of the "modern" method, it can be seen in Table 3 that, of 25 cases having an

"onset time" of less than 48 hours, we had 14 recoveries (56%).

Fever is an important prognostic sign in tetanus, as was observed by Spaeth[51]. The cause of the fever is not certain, but it probably is due to the toxin's direct action on the thermogenic centers, or is the result of frequent and intense muscular spasms. Obviously, concurrent pneumonia or atelectasis increases the temperature and worsens the prognosis. We observed temperatures above 100.4° F. in the first 5 days in 21 of 57 patients, with 5 deaths. In one case a temperature up to 105.8° F. was followed by death within 24 hours.

Another important symptom for evaluation of the disease's seriousness and, at the same time, the treatment's efficacy is the *crisis of apnea*. In 11 patients (19%) who recovered, there were 1 to 14 apneic crises during the development of the disease. They were observed once in 4 patients; twice in 2 patients; 3 times in 1 patient; 4 times in 1 patient; 13 times in 2 patients and 14 times in 1 patient. Since an untreated apneic crisis causes death, we can use its outcome to evaluate the efficacy of treatment.

HIBERNATION. We studied the efficacy of hibernation associated with a skeletal muscle relaxant drug (3-orthotoloxy-1,2-propanediol) in a group of 21 patients, with the assistance of Dr. Bairão and his associates from the Department of Anesthesiology of the Hospital das Clinicas and our assistant, Dr. Amato. To facilitate comparisons, we used the same method of computation as in the "test group" (see Tables 4, 5 and 6).

Method of Treatment. We formulated our "modern" treatment in 1950[55] but scarcity of an injectable form of the muscle relaxant prevented its use as the standard procedure in the Hospital das Clinicas before 1952[56]. During these 2 years the general measures were improved and the method altered qualitatively and quantitatively. Thus, the period from 1950 to 1952 was one of "mixed treatment" and our therapy of tetanus was not standardized until 1952.

TABLE 4.—RELATION BETWEEN AGE GROUPS AND MORTALITY

(HIBERNATION)

Age (years)	*No. of Cases*	*Deaths*	
		Before 48 Hours	*After 48 Hours*
1 to 5	1	0	1
6 to 10	5	2	0
>10	15	5	3
Total	21	7	4

TABLE 5.—RELATION BETWEEN LOCALIZATION OF FOCUS AND MORTALITY

(HIBERNATION)

Focus	*No. of Cases*	*Deaths*
Lower extremities	17	8
Upper extremities	2	1
Unknown	2	2
Total	21	11

TABLE 6.—RELATION BETWEEN "ONSET TIME" AND INCUBATION PERIOD TO MORTALITY.

(HIBERNATION)

No. of Cases	*"Onset Time" (hours)*	*Inc. Period (days)*	*Mortality (%)*
5	>48	..	20
12	<48	..	58
4	Unknown	..	75
4	..	1–5	75
5	..	6–10	40
8	..	>10	37
4	..	Unknown	75

Because most changes in tetanus are reversible (Baker[6]), it is of the utmost importance to prevent death within the first week. After this critical period, organic and functional recuperation of the altered tissues, particularly the nervous tissue, can be expected.

The "modern" treatment can be considered in two principal parts:

a) Specific treatment; including the *focus* and the *immunity* (passive and active).

b) Nonspecific or symptomatic treatment; including *sedation, muscular relaxation, antibiotics and general measures.*

TREATMENT OF THE FOCUS. The suspicious focus must be widely debrided to exclude all conditions producing anaerobiosis, which is essential for the transformation of spores into vegetative forms before multiplication. To prevent the toxin's diffusion into the surrounding tissues, the peripheral region must be infiltrated with antitetanic serum (1,500 to 10,000 I.U.) half an hour before the debridement.

The incision must be wide enough to eradicate all the factors which might lower the local redox potential. According to Fieldes[24], the factors which thus lower the redox potential are: necrotic tissues, suppuration, and foreign bodies. Among these, the more frequent are: thorns, fragments of glass and of metals, particles of earth, dust and catgut thread. Among the drugs capable of lowering the potential are calcium salts, quinine and lactic acid. After debridement the wound must be cleansed with oxidizing liquids (hydrogen peroxide, 1/5,000 potassium permanganate solution, and the like).

Local antibiotics are advocated by Diaz-Rivera *et al.*[20] owing to the bacteriostatic action of penicillin on the tetanus bacillus and pyogenic microörganisms. In some cases the local antibiotics might avoid the debridement but there are contradictory experimental data about the bacteriostatic action of penicillin *in vivo*, despite its accepted action *in vitro*. Thus, Levadite and Vaisman[37] demonstrated penicillin's lack of action in guinea pig experiments. Garlick[29] and Kavitch[33] hold the same opinion.

We favor the use of antibiotics in every case of tetanus because, even if their action on the tetanus bacillus *in vivo* is doubtful, they inhibit the pyogenic microörganisms responsible for local anaerobiosis. They also prevent respiratory complications which frequently cause the deterioration and death of tetanic patients.

The *uterus* is an important focus and almost always is infected from criminal abortion. The uterus serves as a large culture medium for the tetanus bacillus, sometimes associated with the gangrene bacillus which aggravates the disease and increases the mortality. The treatment of the uterine focus has been debated, some authors advocating hysterectomy, others conservative treatment.

Among those who recommend hysterectomy are Denoix and Lenormant[18], no recovery in 4 cases; Allaines and Dubost[4], 2 cases and one death; Lefebvre[36], 3 cases and one death; Barros[8], one patient who survived; and Martins[39], one surviving patient. Opposed to hysterectomy are Ravina[46], one patient who survived without hysterectomy; Weinstein and Beacham[63], 14 cases and 6 recoveries without hysterectomy.

According to Bauchart's compilation[43], in 257 cases of postabortion tetanus the results were: a) 116 hysterectomies with 83% mortality; b) 40 curettages with 75% mortality; and c) 101 cases of conservative treatment with 67% mortality.

Recently we had one patient who survived postabortion tetanus, despite its seriousness, without hysterectomy. We believe that conservative management should be adopted because:

a) Human and animal experiments have shown that amputation of a limb containing a tetanic focus does not prevent death.

b) Hysterectomy is a major operative procedure and such procedures on

tetanic patients should be avoided because of the risk of suture rupture and wound dehiscence during the muscular spasms.

c) Circulating antitoxin can neutralize the toxin from the focus and prevent its ultimate fixation in the central nervous system. Nussensweig *et al.*[43] successfully infiltrated antitetanic serum (60,000 I.U.) into the uterine cervix of one patient. Menendez[41] advocates irrigating the uterine cavity with hydrogen peroxide and antitetanic serum.

d) Penicillin may be effective against the tetanus bacillus (Diaz-Rivera[20] and Weinstein and Wesselhoeft[62]) localized in the uterine focus.

Such strong surgical indications as perforation or abscesses, however, necessitate an operation despite the inconveniences already mentioned.

When the suspicious focus is a surgical suture, either internal or external, we prefer the same conservative therapeutic procedures as in cases of a uterine focus. Recently we observed a case of tetanus after gastroenterostomy, probably due to an infected catgut suture.* The patient survived with conservative therapy.

Although theoretically debridement is important, some statistics do not completely support this concept. Vinnard[61] reports that among 184 debrided cases he had a mortality rate of 36% and among 109 cases not debrided, a death rate of 31.1%. Spaeth[51] believes that debridement does not influence the mortality. Pfuhl and Tranchesi[42] in 91 debrided cases had a mortality of 31.2% and 35.6% of deaths in 44 cases not debrided. Veronesi *et al.*[54] reported 29.8% of deaths in 84 debrided cases and 37.3% in 110 cases not debrided. In this present series we had 25% of deaths in 12 debrided cases and 17% of deaths in 35 cases not debrided.**

We believe that an evident focus should be debrided except for the contraindications already mentioned. This therapeutic measure, however, is less urgent than sedation, muscular relaxation and serum therapy; the latter taking priority over all other measures.

IMMUNOTHERAPY. False concepts and ideas about immunotherapy still exist. Thus intensive serum therapy is based on the incorrect clinical concept that the greater the amount of serum the greater the percentage of survival.

The value of serum therapy was established by animal experiment and extensively proved by clinical experience. Before the discovery of antitetanic serum by Behring and Kitasato, in 1890, tetanus mortality was about 85% (Cole[14]). As a result of the discovery of serum therapy the mortality was reduced to 30 to 70%, with an average of 45 to 50%. Antibiotics, sedatives, modern muscle-relaxants, and other modern general measures make it difficult to evaluate the real efficacy of serum therapy alone today.

Unfortunately, after the onset of clinical tetanus, serum does little or nothing to abolish the symptoms already present. Animal experiments, like those of Abel and Chalian[1], established the role of antitoxin in tetanus and the extent to which it prevents death. They concluded that antitetanic serum is inefficient in diminishing or abolishing the symptoms already present in animals and in humans, if administered after the fixation of one or more minimal lethal doses of the toxin in the central nervous system. In such conditions the serum does not save the patient's life and, consequently, must

*Cultures of pieces of the catgut and the drain were negative when tested by Dr. Toledo Mello, of the Department of Microbiology of the Medical School, University of São Paulo.

**In 10 cases there was no reference to debridement. This measure is usually undertaken at the hospital's first aid station.

not be considered as having a specific curative action. Many human experiments corroborate these results.

In 1941, Spaeth[52] titrated the circulating antitoxins and showed that doses from 35,000 to 50,000 I.U. were large enough to treat any form of tetanus. In the presence of serious asphyxiant spasms, the prognosis is favorably influenced, not by the serum therapy, but by the antispasmodic measures and the prevention or treatment of pneumonia and exhaustion.

In 1951, our interest in the standardization of preventive and "curative" serum therapy led us[57] to titrate periodically the circulating antitoxins following a single dose of serum. The results are reported in Tables 7, 8 and 9.

Table 7 shows that the minimal adequate titer (0.1 unit per ml.) persisted 10 days after the administration of 3,000 I.U. This result led us to conclude that this dose provides no adequate protection after 10 days.

In Table 8 are reported the results of the titrations of the circulating antitoxins after the administration of 100,000 I.U. (50,000 intravenously and 50,000 intramuscularly) in a single dose to 4 *nontetanic* individuals. After 28 days, the titer was still 5 times higher than the minimal adequate titer (0.1 unit).

Table 9 shows the titrations of circulating antitoxin in 6 *tetanic* patients, of whom 5 received 100,000 I.U. and one, 150,000 I.U., in a single dose, half intravenously and half intramuscularly.

TABLE 7.—CIRCULATING TETANUS ANTITOXIN AFTER 3,000 I.U. INJECTION TO NORMAL PERSONS

Patient	*Before*	*After 5 Days*	*After 10 Days*	*After 15 Days*
J. M.	—0.001	+0.1 —0.3u	+0.1 —0.2u	+0.01 —0.1u
A. F. B.	—0.001	+0.5 —1	0.1u	+0.01 —0.1
L. P.	—0.001	+0.3 —0.5u	+0.2 —0.5u	+0.1 —0.2u
A. M.	+0.1 —0.5	0.5u	0.2u	+0.1 —0.2u
J. A. B.	—0.001u	+0.1 —0.5u	+0.2 —0.3u	0.1u

TABLE 8.—CIRCULATING TETANUS ANTITOXIN AFTER 100,000 I.U. INJECTION TO NORMAL PERSONS

Patient	*Before*	*After 7 Days*	*After 14 Days*	*After 21 Days*	*After 28 Days*
J. G. N.	—0.001u	5u	+2 —3u	1u	0.5u
B. F. O.	—0.001u	5u	+2 —4u	+0.5 —1	0.5u
A. M. G.	—0.001u	5u	2u	+0.5 —1u	0.5u
F. S. O.	—0.001u	5u	2u	+0.5 —1u	+0.5 —1u

TABLE 9.—CIRCULATING TETANUS ANTITOXIN AFTER INJECTING 100,000 OR 150,000 I.U. TO TETANIC PATIENTS

Patient	*Before*	*After 7 Days*	*After 10 Days*	*After 21 Days*
W. S.	—0.05u		+5 —10u	+2 —4u
L. P.	0.5 (*)		5u	3u
O. P.	—0.001u	+10 —20u	+5 —10u	+1 —2u
M. O. R.	+0.001 —0.01	+3 —5u	+1 —2u	
M. S. T.	—0.001u	5u	2u	1u
M. D. B.	—0.001u	20u (**)	4u	+2 —4u

* Received A.T.S. before the admission (unknown amount)
** Received 150,000 I.U.

After 21 days, all the patients still showed titers *10 to 30 times* the minimal effective titer.

The titers in *tetanic* patients were 2 to 4 times higher than those in *non-tetanic* patients, although the latter had no toxin to be neutralized. This suggests that the patient forms antibodies as the disease develops. Probably the antibodies are formed late because the antitoxin titers were low before the administration of serum. The patient's antibodies (active immunity) have the same fate as those administered (passive immunity), since the antitoxin titers progressively diminished in both groups, and it is well known that tetanus does not provide lasting immunity.* Despite the existence of titers above the adequate minimum (0.1 I.U. per ml.) for longer than 3 weeks after an injection of a single dose of 100,000 I.U., it was necessary to demonstrate by means of clinical trials that such doses are effective and to compare their results with those obtained with larger doses.

In 1937, Huntington, Thompson and Gordon[32], analyzing 642 cases, were not impressed by the efficiency of the serum in decreasing the mortality (63% of their cases). Spaeth[51], in 1941, expressed the opinion that the ideal doses are those from 40,000 to 60,000 I.U. In 1942, Firor[25] stated that 50,000 I.U. are sufficient to neutralize the toxin that might be circulating. In 1945, Vinnard[61] related that he could not lower mortality rates by administering doses larger than 100,000 I.U., and that the rate was even higher when larger doses were administered. In 1945, Pratt[45] analyzing a series of 56 cases, concluded: "It was not evidenced that amounts of toxin over 80,000 I.U. were more efficient than those of 30,000 I.U."

In 1948, Neves and Tranchesi[42], in the Hospital das Clinicas, analyzed 136 cases having a mortality rate of 37.5% after receiving doses of 400,000 to 700,000 I.U. and concluded: "There was no improvement in the mortality rate in spite of the large doses of antitetanic serum administered." In 1954, Crespo[17], analyzing 70 patients to whom he administered doses no larger than 10,000 to 20,000 I.U. intramuscularly, emphasized that such small doses were compatible with the lowest mortality rate he observed (27% in his group). In 1954, Diaz Rivera, Trilla and Pons[19] treated 15 patients with 80,000 I.U. (40,000 intravenously and 40,000 intramuscularly) and 10,000 I.U. daily for 3 days, obtaining a mortality rate of 13.3%.

If we compare the results obtained in the Hospital das Clinicas by large doses (37.5% mortality rate in 136 cases) with those obtained by the administration of only 100,000 I.U. (18.2% mortality rate in 236 cases) it should be clear that antitetanus serum does not have any other action than that already attributed to it.

ROUTE OF ADMINISTRATION OF THE ANTITETANIC SERUM. *Accidents.* Routinely, we use both intravenous and the intramuscular routes, administering half the dose by each route. There are patients, however, who cannot receive, under any circumstance, antitetanus serum intravenously owing to the possibility of anaphylaxis. These include patients who were once sensitized by heterologous serum and those who have a history of allergy, such as bronchial asthma, urticaria, eczema, Quincke's edema, or allergic rhinitis.

Sometimes, in spite of negative ocular or skin tests, anaphylactic shock may occur. To prevent such crises, we add 1 ml. of 1:1,000 aqueous solution

*All of our patients receive the first dose of tetanus toxoid in the convalescence period before leaving the hospital and are instructed to return one month later for the second dose.

of epinephrine to the antitetanic serum dissolved in 250 ml. of 5% solution of glucose or in a mixture of glucose solution and isotonic sodium chloride solution, administered intravenously.

Intrathecal administration is dangerous and is not superior to other routes. It is contraindicated by experienced authors such as Pratt[45], Dietrich[21], Spaeth[51] and Vinnard[61].

Muscle Relaxation. The most important part of the treatment of tetanus is adequate and efficient muscle relaxation but it is difficult to determine to what extent muscle relaxation contributes to the survival of the tetanic patient. As early as 1940, Firor, Lamont and Shumaker[26] observed that tetanic dogs receiving Nembutal and Avertin in the average dose required to overcome convulsions died more rapidly than the control animals which did not receive such drugs.

Depression of the respiratory center directly by tetanus toxin or, according to Firor *et al.*[26], by the action of a secondary "lethal substance" originated in the nervous system, is one cause of death in tetanus. It is easy to understand that drugs which tend to depress the respiratory center, as well as to relax muscles, can hasten death by acting synergistically with the toxin.

An ideal drug would abolish muscular spasm without depressing the respiratory center, would have no untoward effects, would offer a wide margin of safety between the therapeutic dose and the paralyzing one, and would be easily administered for a minimum of 7 to 10 days. Such an ideal drug does not exist.

Among the drugs more frequently used are barbiturates, chloral hydrate, curare and its derivatives, Avertin, and Mephenesin or 3-ortho-toloxy-1,2 propanediol*, most recently with hibernation.

Some of these, such as chloral hydrate and Avertin, cannot be used to manage apneic crises. They must be used with other drugs that can be rapidly administered intravenously. Curare and hibernation are not beneficial in such emergencies. According to Dietrich[21] curare is more dangerous than useful, and Firor[27] states that it failed to lower the mortality rate in the United States.

We believe that 3-ortho-toloxy-1,2 propanediol is the drug of choice, administered according to our method, even though it does not completely solve the problem of tetanic intoxication. Some cases do not respond satisfactorily to any muscle relaxant drug. Such cases present the most difficult problem, namely, to obtain relaxation without paralysis. Still other patients do not require muscular relaxation and die of respiratory center failure with no apneic spasms (encephalitis-like).

Good results have been obtained with 3-ortho-toloxy-1,2 propanediol throughout the world since 1947, when Belfrage[9] used it for the first time. Among those reporting good results are Torrens, Edwards and Wood[53], Armstrong, Ward and Pask[5], Alamanada and Roy[3], McDonald[40], Godman and Adriani[30], Bello and Marques[10], Bandi[7], Veronesi and Meira[55], Boles and Smith[12], Biehl and Helm[11], Diaz-Rivera, Trilla and Pons[19], and more recently, Adriani and Kerr[2]. The methods of administration and doses of the drug were not alike in the various reports. Our opinion agrees with that in a great part of the specialized literature: the drug acts effectively when administered intravenously, the results being less effective when it is given orally.

The intravenous drip of a water and saline solution of the muscle relaxant drug with glucose was first used by McDonald[40] in 2 children who recov-

*Tolserol—E. R. Squibb & Sons.

ered from tetanus. In 1950, we[55] occasionally tried the method because at that time there was an insufficient quantity of the drug in injectable form. We started using it routinely in 1952[56] obtaining the results which are the subject of this report.

In 1954, Diaz-Rivera *et al.*[19] used the method we prefer in 4 of the 15 patients described in their report and stated that "Mephenesin seems to be the drug of choice in moderately severe tetanus, when the spasms are not very frequent. The drug was very useful and probably was responsible for the recovery of 6 patients when used for the treatment of laryngeal spasms."

This method was employed in 236 cases of tetanus in the Hospital das Clinicas of São Paulo during 3 successive years.* We believe that the muscular relaxation obtained with it prevents the hazards of deep sedation; its respiratory complications and its depressive action on the respiratory and coughing centers which frequently cause death. Its remarkable action is shown by the control of apneic crisis when a 2% solution of the drug is administered intravenously.

We observed, from the beginning, that it was absolutely necessary to maintain constant vigilance, *day and night*, in order to carry out, without delay, the measures constituting the therapeutic scheme.

DOSES AND MAINTENANCE, TECHNIQUES OF ADMINISTRATION. The amount of 3-ortho-toloxy-1,2 propanediol used depends upon the body weight, individual requirements, and the severity of the disease, the daily doses varying from 8 to 24 gm.

The solution containing the muscle-relaxing drug is prepared by adding to each 500 ml. flask of 5% glucose solution 3 to 6 ampules of 3-ortho-toloxy-1,2 propanediol. Each ampule contains 1 gm. of the relaxing drug as a 2% solution in 50 ml. of saline solution so that it is unnecessary to use glucose-saline solution as the vehicle. In order to provide the vitamin requirements while the patient cannot eat, we add to each vial of the muscle-relaxing solution, 25 mg. of thiamine and 100 mg. of ascorbic acid.

From two to four flasks are used per 24 hours, since each contains 600 to 800 ml. of solution. The velocity of the drip is adjusted to the necessities of the moment, between 30 to 60 drops a minute. The duration of the drip varies according to the individual characteristics of the case and, in some instances, it must be continued for 8 to 10 successive days. The intravenous therapy is discontinued gradually in order to observe whether muscular spasms will reappear.

If no spasms occur during 24 to 48 hours on small doses of the drug (1 or 2 gm. in 600 ml. of solution) we withdraw it completely. Administration is resumed promptly if spasms reappear.

The intravenous route presents some problems. Relaxation is a direct function of the drug's concentration in the blood, so that injection directly into the vein must be continuous. When the needle is dislodged, spasmodic contractions increase and may cause apnea and death. Injection through an intravenous polyethylene tube prevents such accidents, particularly in the more severe cases. Neither the needle nor the polyethylene tube should remain in the same vein for more than 48 hours, since the drug frequently causes phlebitis.

MANAGEMENT OF APNEIC CRISES. Dur-

*By July, 1955, the number of cases treated by this method had reached more than 300 and the same efficacy had been observed.

ing an apneic crisis, muscular relaxation must be induced within a few seconds. *Within one or two minutes an untreated apneic crisis becomes irreversible.* The physician cannot be present continuously, day and night, so we have taught the nurses of the Hospital das Clinicas the general measures to be taken in such crises and have given them the authority and responsibility to manage the acute episode. A special nursing team to treat tetanic patients has proved a great advantage.

The steps to be taken when an apneic crisis begins are: a) Speed the flow of the relaxing solution. b) Inject immediately a 2% solution of the relaxing drug by way of the rubber tube already connected to the intravenous needle. The amount varies from 20 to 50 ml. c) If these measures are ineffective and no signs of respiratory activity appear, use the mask-type mechanical resuscitator. If this is not available, begin manual artificial respiration immediately. Other respirators are useless, since they require too long a period to put into operation.

The muscle-relaxing drug must be administered within 15 seconds of the start of the apneic crisis and the necessary materials must be already prepared on a table in the patient's room. In such circumstances the presence of another nurse is helpful.

We conceived, with the assistance of Dr. Kurt Kloetzel, a procedure that facilitates the rapid administration of the solution. The rubber tube to the intravenous needle is connected to two bottles by means of a Y-shaped glass tube. The number 1 bottle contains a weak solution of the relaxing drug (less than 1%) and the number 2 bottle contains a more concentrated solution (2%) to be used in apneic crises. To prevent crystallization, this solution is kept warm by means of a heating coil introduced into the bottle. At the onset of a crisis the valve from the number 2 bottle is released and that from the number 1 bottle is closed. When the crisis is passed, administration of the weaker solution in number 1 bottle is resumed. As a safety measure we allow the number 2 solution to drip for 5 to 10 minutes after each crisis.

Sedation. The 3-ortho-toloxy-1,2-propanediol is a weak sedative at best, so we use sedatives to diminish central nervous system excitability and so avoid the continuous hypertonia and paroxysmal spasms.

The most suitable sedative must be chosen; it must provoke neither narcosis nor depression of the bulbar centers, mainly the respiratory and the coughing centers. Unfortunately, the several sedatives used to treat tetanus exert such untoward effects, so that we use small amounts of sedative. Our object is only to supplement the muscle relaxant's action, so that small doses of barbiturates or rectal chloral hydrate suffice. Barbiturate doses are adjusted by age and body weight, never exceeding 0.10 to 0.30 gm. every 24 hours. Rectal chloral hydrate dosage is 1 to 2 gm. every 8 hours. In order to avoid cumulative action, the enema, like any sedative, should not be repeated while the action of the preceding dose is still evident.

SEMI-HIBERNATION. Hibernation was used for 21 patients to evaluate its muscle-relaxing and sedative action. We subsequently adopted what we could call "semi-hibernation" combined with 3-ortho-toloxy-1,2-propanediol. We concluded from the analysis of these cases that:

1) In the mild cases, good sedation and muscle-relaxation were obtained. 2) In the severe cases, apneic spasms were not relieved and the results were less satisfactory than those obtained with 3-ortho-toloxy-1,2-propanediol used with small doses of barbiturates

or chloral hydrate. 3) Confusion, hallucination, delirium and incoordination sometimes occurred as the hibernating drugs were withdrawn. 4) Paradoxical temperature increases and sudoresis sometimes followed reduction in the doses of the hibernating "cocktail." 5) The mortality rate in this group of 21 cases was 52.3%.

Considering only the severe cases, we obtained the following results: a) Fifty-eight per cent mortality rate in 12 cases considered severe with an "onset time" of less than 48 hours. A similar severely ill group, treated with 3-ortho-toloxy-1,2-propanediol plus barbiturates, had a mortality rate of 44%. b) Seventy-five per cent mortality rate in 4 patients with an incubation period from 1 to 5 days. In a similar group, we had a 25% mortality rate among 12 patients using 3-ortho-toloxy-1,2-propanediol plus barbiturates.

Hematological examinations of 8 hibernated patients showed no changes other than those frequently observed in tetanic patients, namely, leukocytosis with a shift to the left of neutrophils and eosinophilia. *Urinalysis* of 7 patients was normal in 4 and positive for *hemoglobin* in 3. *Blood urea determinations* in 5 patients showed elevated values in 2 patients who died (41 and 85 mg. per 100 ml. respectively). *The carbon dioxide capacity of the plasma* in 3 patients was normal. Laborit[35] has the same ideas we have concerning hibernation in tetanus.

The drugs we used every 24 hours for the hibernating "cocktail" were chlorpromazine, 50 to 150 mg.; Phenergan, 50 to 150 mg.; Dolantina, 50 to 100 mg.; B Complex, 2 ampuls; and Vitamin B_1, 100 mg. The solutions were given in 5% glucose in water or in glucose and saline. A 2% solution of 3-ortho-toloxy-1,2-propanedol was added in a dose of 4 to 6 gm. per liter of the "cocktail."

We maintained our patients in a state of semihibernation for from 18 hours to 15 days, using the same specific treatment (antitetanic serum) and general therapeutic measures as in the other groups studied.

We believe that a partial hibernation may be indicated in the cases of exaggerated psychogenic excitation in order to interrupt the excitation-spasm-excitation circle. We do not expect favorable results when spasms and apneic crises develop during hibernation.

Antibiotics. We used penicillin alone or with streptomycin, the doses varying according to the severity of the illness and the nature of the focus. In severe cases with a large focus such as the uterus we administered 100,000 and 200,000 units of penicillin every 4 hours and gave 400,000 units of repository penicillin every 12 or 24 hours in the less serious cases.

Nourishment. The method described above provides the patient sufficient nourishment, electrolytes, and liquids to maintain vital function until he can swallow. If normal nourishment by the oral route cannot be established within one week, we administer plasma or blood transfusion.

We avoid alimentation through a feeding tube, particularly in severe cases, because contact of the tube with the pharynx and epiglottis may provoke spasms by reflex action. Besides this contraindication, regurgitation of undigested food during spasms may produce aspiration pneumonia, especially in infants.

All severely ill tetanus patients must be fed parenterally during the spasmodic phase of the disease. To insist on administering nutrients orally during this period is to risk the patient's life by provoking spasms and apnea. Only after the spasms cease can oral administration of nutrients be tried

cautiously, beginning with liquids and continuing with porridge.

Oxygen was used for 1) cyanosis, 2) elderly people or cardiac patients, and 3) concurrent respiratory diseases such as pneumonia or atelectasis.

Aspiration of secretions must be prompt, so an aspirator was always kept in the patient's room to avoid the danger of suffocation produced by the secretions.

Tracheotomy was indicated for spasm of the glottis. Our experience does not encourage us to undertake tracheotomy when the patient's condition is precarious because the mortality rate is high. An earlier study of 200 cases of tetanus[34] in children up to 14 years old revealed 11 deaths in 12 tracheotomized patients (91.7%). The tracheotomy cannot be considered the sole cause of death because the operated group contained the more severe cases and the operation was performed when the children were almost *in extremis*.

In our group of 57 cases, tracheotomy was performed only once and that unsuccessfully. Satisfactory muscular relaxation restricts the surgical indications to those cases in which secretions are excessive and cannot be expelled by the patient nor aspirated by an aspirator.

Nursing Care. Besides the all-important role of the nurse responsible for the tetanic patient, chiefly during apneic crises, some aspects of the nursing care must be emphasized: 1) The tetanic patient must not be moved during the spasmodic stage and hygienic care must be minimal. 2) The respiratory rhythm must be closely observed to detect an apneic crisis. 3) The patient must be catheterized if he does not void every 8 hours.

Other Measures. Trendelenburg's position is indicated when secretion is excessive. Atropine, 0.25 mg. every 8 to 12 hours, may help reduce the amount of secretion, but sometimes thickens the secretions and prevents their elimination or aspiration. The tongue must be protected against biting and consequent hemorrhages. Antipyretics may be used when the temperature is 102° F. or more.

Physiotherapy. Muscular relaxation by means of heat and passive reeducation are indicated when the patient is in the phase of residual hypertonia with no paroxysmal spasms, generally 15 to 20 days after admission. The patient should not be allowed to walk alone the first few days after leaving the bed because falls are frequent during this residual hypertonic state. Physiotherapy and orthopedic measures are indicated to correct spinal deformity.

EVALUATION OF COMPLICATIONS ATTRIBUTED TO THE METHOD OR TO THE DISEASE. In 7 of our 57 patients we observed mild *phlebitis* which disappeared readily and was caused by the drug's chemical irritation.

The more frequent gastrointestinal complaints were *abdominal pain* (9 times in 57 cases) and *nausea* (4 times in 57 cases). These may be due to the disease itself (gastric lesions[44], spasms of the rectus abdominis, vertebral deviation) or to gastric irritation by the drug administered orally.

Slight *hemoglobinuria* was observed in 3 of the 57 cases. It is caused by the drug administered parenterally. In a rough evaluation of the blood picture in 15 of the 57 cases, we observed only leukocytosis with a shift to the left of the neutrophils, and eosinophilia. We did not observe anemia which could be attributed to the drug.

Calcium determination in the blood gave us approximately normal levels in 7 of our 57 cases. Bonino[31] obtained normal blood values of *calcium*, *potassium*, *chlorides* and *creatinine* in tetanic patients.

Electrocardiograms made in 12 cases were normal in 9. Of the remaining 3 patients, one, 21 years old, showed primary alterations of the T wave; another, 8 years old, had enlarged P waves, notched in D_1; and the last, 19 years old, showed primary anomalies of the T wave, suggesting myocardial involvement. Myocardial damage has been ascribed both to 3-ortho-toloxy-1,2-propanediol (Cowen[15] and Diaz-Rivera, Trilla and Pons[19]), and to the tetanus toxin (Pelloja[44]).

Skeletal Changes. We studied roentgenographically the spinal column of 47 tetanic patients who recovered and whose ages were from 15 days (tetanus neonatorum) to 50 years. The findings are summarized in Table 10.

TABLE 10.—RELATION BETWEEN AGE AND VERTEBRAL ALTERATIONS

Age	*No. of Cases*	*Radiologic Findings*
Up to 2 months	12 (umbilical)	None or very slight
1 to 10 years	11	9 (81.8%)
11 to 20 years	15	14 (93.3%)
+ 20 years	9	1 (11.1%)
Total	47	

Almost all patients between one and 20 years of age showed roentgenographic evidence of vertebral alterations. The films, studied with the assistance of Dr. Flavio Pires Camargo, of the Orthopedic Clinic, and Dr. Dacio Pinheiro, of the Pediatric Clinic, Medical School, University of São Paulo, showed the most important alterations to be flattening, sometimes to a considerable extent, of the dorsal vertebrae, especially those from D_4 to D_7. Although less accentuated, the dorsal vertebrae (D_1, D_2, D_3, and D_8) were altered in many cases.

The flattening was usually localized on superior vertebral surfaces, sometimes with the formation of a notch in the middle of the superior contour of the vertebrae. Condensation of the vertebral structure was very frequent, chiefly in the more compressed region. Such alterations were accompanied by kyphosis and sometimes by "pectum carinatum" (see Figs. 1, 3, 4 and 5), the kyphosis being more evident roentgenographically than clinically. It sometimes was almost imperceptible on physical examination. In several patients, flattening was so marked that the vertebra was reduced to less than one-third of its height and was wedge-shaped with the base posterior. The intervertebral spaces were not evidently altered.

The clinical evolution of these cases is being followed, but it is still too early to evaluate the results. After one to 12 months, the follow-up study shows that the clinical evolution is slow, with partial or no regression of the flattening (see Figures).

Neonatal patients with umbilical tetanus do not show alterations of the vertebral structure or, at most, very slight flattening.

Our findings agree with those of Roberg[47] and Dietrich, Karshner and Stewart[22]. Clinically, there is very little or no local pain. When examining a tetanic patient with accentuated flattening of the dorsal vertebrae one has the impression that he has "contracted" the neck and raised the shoulders.

COMPARISON OF THERAPEUTIC METHODS IN THE HOSPITAL DAS CLINICAS. In Table 11 it is possible to compare the therapeutic efficacy of the various regimens used to treat tetanus in the Hospital das Clinicas.

The "old" treatment, used from 1944 through 1949, had an average mortality rate of 27.2% in the 294 cases, but there was a progressive decrease each year except during 1948. Almost all the patients received rectal chloral

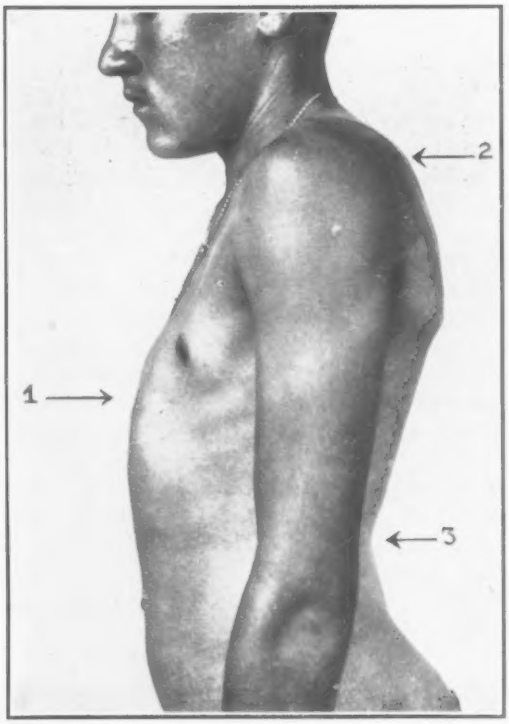

Fig. 1.—Case J.B.N. Photograph taken 2 months after the acute stage. Arrows indicate: 1, Pectum carinatum. 2. Dorsal kyphosis. 3, Lumbar lordosis.

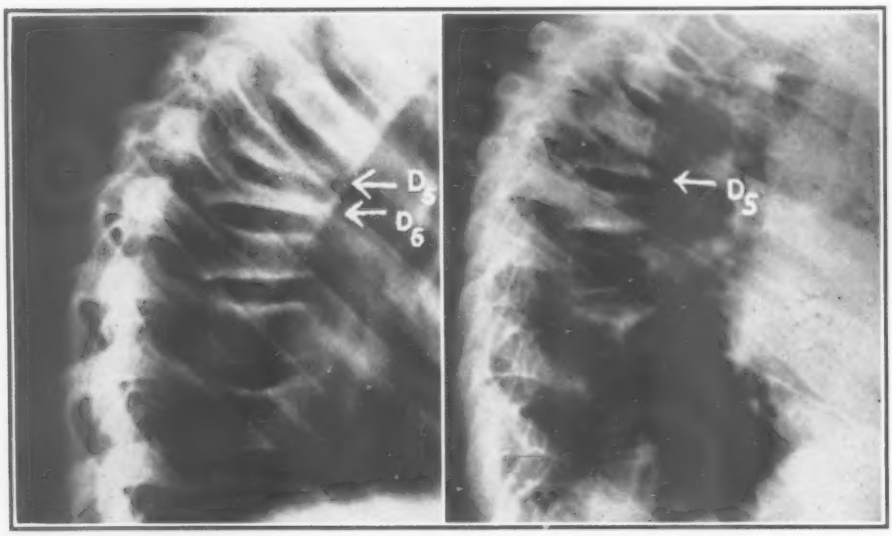

Fig. 2. Fig. 3.

Fig. 2.—*Case S.A.* 11 years old. Radiogram 18 days after admission. Accentuated wedge-shaped flattening of the dorsal vertebrae 5 and 6 and condensation of the vertebral structure are seen.

Fig. 3.—*Case J.B.N.* 14 years old. Radiogram 24 days after admission. Accentuated rounded kyphosis, and flattening of several dorsal vertebral bodies, chiefly D_5, which shows a reduction of one-third its height.

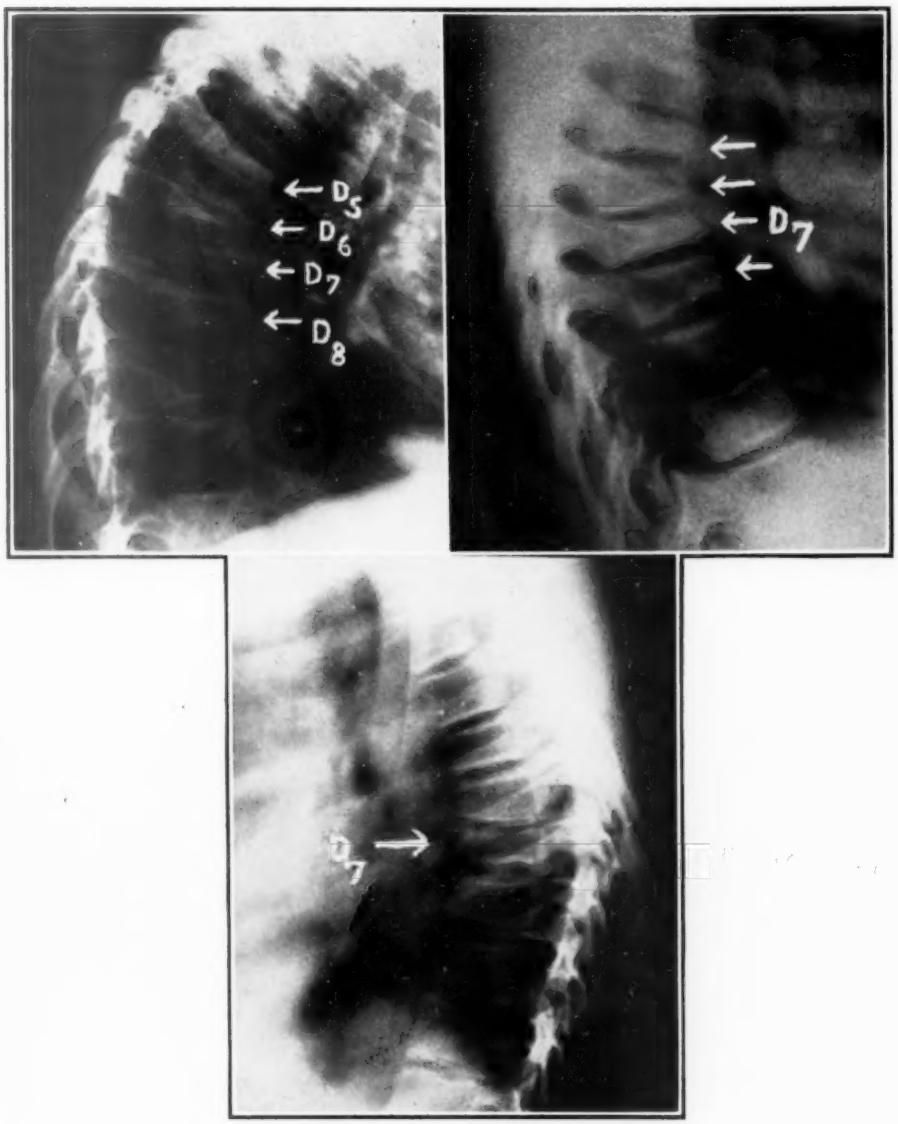

Fig. 4*A*. *Case N.G.* 15 years old. Radiogram 33 days after admission. Mid-dorsal kyphosis and wedge-shaped flattening of D_5, D_6, D_7 and D_8, chiefly D_7, without break in cortical continuity. There is diffuse condensation chiefly of the anterior portion of the vertebrae. Disks are normal size.

B, *Case N.G.* Same case 49 days after first radiogram and 82 days after admission. There is a tendency toward reconstruction attributable to the epiphysis and vertebral bodies. There is still flattening from D_5 to D_8.

C, *Case N.G.* Same case, one year after acute stage. Tendency toward reconstruction of D_7.

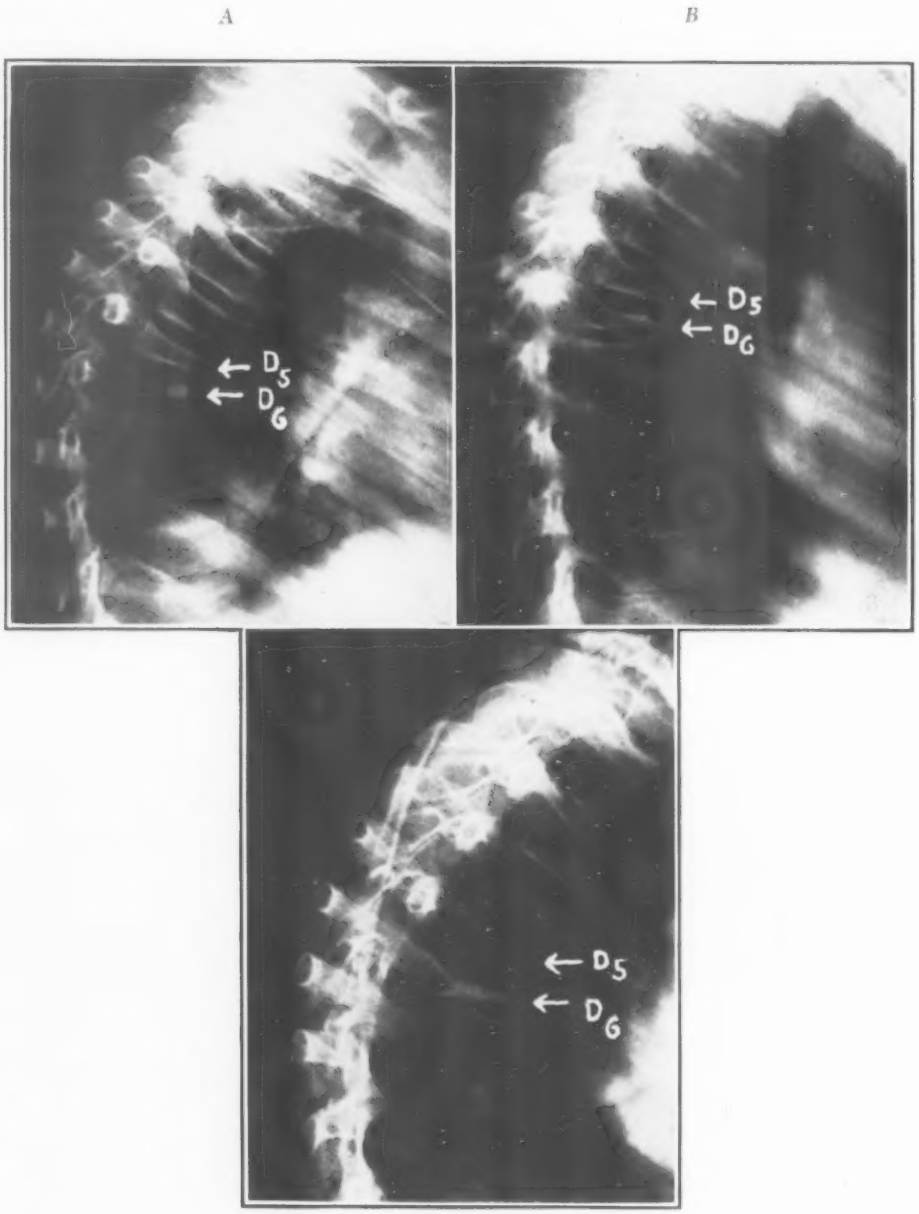

Fig. 5*A*. *Case M.D.V.M.* 10 years old. Radiogram 25 days after admission. Accentuated flatness of D_5 and D_6. Dorsal kyphosis.

B, *Case M.D.V.M.* Same case radiographed 3 months after admission. Practically the same appearance.

C, *Case M.D.V.M.* Same case radiographed 9 months after admission. Flattening of D_5 and D_6 still present. Dorsal kyphosis.

hydrate, barbiturates (chiefly Sonifeno) and magnesium sulfate (Baker[6]). Antitetanus serum was used in doses of 400,000 to 700,000 I.U. (Neves and Tranchesi[42]). Sulfonamides and penicillin were employed routinely.

The "mixed" treatment period of 1950 and 1951 included 141 patients, with a mortality rate of 25.9%. During this period the new standardized therapy scheme was introduced, but could not be used for all tetanic patients.

Our "modern" regimen was used with only minor variation for the 236 cases in the 1952 through 1954 group and for another 20 in the first 5 months of 1955. These latter, with the last 37 cases in 1954, constitute our "test group" of 57 patients. From 1952 through 1954, there was an average annual admission rate of 78, the highest of the groups, and a mortality rate of 18.2%, the lowest. The severity of these cases was comparable to that in earlier groups.

Taking into account the factors used to evaluate the severity of the illness, namely, age, incubation period, onset time, apneic crises, and temperature, the "modern" treatment using an intravenous muscle relaxant was superior to the "old" therapy, especially in the most serious cases and in the "test group." The mortality rate for the latter was 21% and of this only 10.5% (net mortality) was contributed by patients surviving beyond the first 48 hours of hospitalization.

Comparable statistics for other hospitals are given in Table 12. Vinnard[60] reported a mortality rate of 41% in the United States prior to 1950. The lowest North American death rate was that of Vener and Bower[59] with 29

TABLE 11.—ANNUAL TETANUS ADMISSION AND MORTALITY RATES IN THE HOSPITAL DAS CLINICAS OF SAO PAULO

Year	*No. of Cases*	*Method of Treatment*	*Mortality Rate*	
			Before 48 Hrs.	*After 48 Hrs.*
1944	10	"Old"	20%	20%
1945	38	"	16%	21%
1946	52	"	13%	13%
1947	41	"	7%	12%
1948	86	"	7%	26%
1949	67	"	3%	15%
1950	80	"Mixed"	12%	10%
1951	61	"	16%	13%
1952	84	"Modern"	11%	10%
1953	74	"	11%	12%
1954	99	"	7%	13%
Total	692		10%	14.5%

TABLE 12.—TETANUS MORTALITY RATES IN VARIOUS COUNTRIES

Author	*Country*	*No. of Cases*	*Mortality Rate (%)*
Vinnard[60]	U. S. A.	352	45
Vener and Bower[59]	U. S. A.	100	29
Kirtley[34]	U. S. A.	60	46.6
Pratt[46]	U. S. A.	56	43
Crespo[17]	Cuba	70	27
Gonzalez and Floriani[31]	Argentina	367	40
Salveraglio and Ebola[48]	Uruguay	158	52
Spaeth[51]	U. S. A.	96	35
Smathers and Weed[50]	U. S. A.	82	60
Silverthorne[49]	Canada	70	47
Creech, Woodhall and Ochsner[16]	U. S. A.	184	35
Adriani and Kerr[2]	U. S. A.	100	32
Dopff and Perez[23]	Spain	50	28
Veronesi (*)	Brazil	692	24.5
Veronesi (*)	Brazil	236	18.5

(*) Mentioned in this paper

deaths in 100 consecutive cases reported in 1941.

Such factors as variations in bacillary strains, season, age groups and severity of the illness may alter the mortality rate in tetanus. We believe, therefore, that to be of value for comparative studies, reports should cover more than 50, and preferably more than 100 cases analyzed as to the severity of the disease.

Summary. Tetanus is common in Brazil, 692 cases having been admitted to the Hospital das Clinicas during 10 years (1944 through 1954). On the "old" therapeutic regimen of sedation and antitetanus serum, the mortality rate was 27.2%.

A "modern" regimen of continuous intravenous Mephenesin (3-ortho-toloxy-1,2-propanediol), supplementary barbiturate or chloral hydrate sedation, antibiotics, intravenous alimentation, and small doses of antitoxin 100,000 I.U. was administered by specially trained nurses. In use since 1952, this therapy has reduced the mortality rate to 18.2% in the last 236 consecutive cases. Drug-induced hibernation, added to this regimen in 21 cases, raised the mortality rate to 52.3% and hence is recommended only for the few patients with exaggerated emotional reactions.

Apneic crises demand special attention with constant observation to detect and treat them during the first 15 seconds of the episode. Such crises generally respond to an immediate increase in the intravenous administration of Mephenesin until the episode passes.

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(Interlingua on page 694)

MEASUREMENTS OF MECHANICAL AND ELECTRICAL EVENTS OF THE CARDIAC CYCLE

I. EFFECT OF TACHYCARDIA, PRE-ANESTHETIC MEDICATION, AND DI-ETHYL ETHER ANESTHESIA

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Since the introduction of di-ethyl ether as an anesthetic agent more than a century ago, a considerable number of observations have been made of the effect of this drug on the cardiovascular system. The majority of these observations have been concerned with two particular aspects of cardiac activity, output (Blalock[4,5], and Brewster, Isaacs and Wain-Anderson[7]) and rhythm (Bhatia and Burn[3], Cattell[9], Goodman and Gilman[11], Harris[12], Hill[13], Kurtz, Bennett and Shapiro[17], Marvin and Pastor[20], Meek, Hathaway and Orth[21], Milowsky and Rovenstine[23]). Respiratory paralysis usually precedes the onset of frank cardiac failure, but certain definite cardiac effects of ether are known to result from its use in clinical dosage, particularly shifting pacemaker, extrasystoles, and diminished cardiac output. The present investigation was designed to elucidate any additional effects of ether upon the heart by means of an analysis of the relationship between certain mechanical and electrical events of the cardiac cycle. A corollary study of the effect of a change in cardiac rate on these relationships was also made.

Material and Methods. Thirty-five young adult men and women were studied: clinical examination of the heart, teleoroentgenogram, and twelve lead electrocardiograms were normal in all subjects. Simultaneous records of the electrocardiogram and phonocardiogram, and also of the electrocardiogram and carotid pressure tracing were obtained on a Sanborn-Twin-Beam photographic recorder. Lead II of the electrocardiogram, and the logarithmic phonocardiogram over the mitral area were employed; the carotid tracing was obtained by a capsule and piezo-electric crystal recorder (Cambridge Co.). A paper speed of 75 mm./sec. was employed and the arithmetic means of approximately 30 complete consecutive cardiac cycles were used for each observation.

The following time intervals were measured:

1. Q wave—1st tone: The interval between the first deflection of the QRS complex and the first of the major vibrations of the first heart sound.
2. 1st tone—2nd tone: The interval between the first of the major vibrations of the first heart sound and those of the second heart sound.
3. Q wave—carotid arterial pulse rise: The interval between the first deflection of the QRS complex and the point of com-

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mencement of rapid rise of the carotid arterial pulse tracing. No correction for the time for passage of the wave from the left ventricle to the carotid artery (approximately 0.02 second) was included, for since comparison was made on the same individual, the error was considered constant in this and in the subsequent interval, 1st tone—carotid pulse rise.

4. 1st tone—carotid pulse rise: The interval between the first of the major vibrations of the first heart sound and the point of commencement of rapid rise of of the carotid arterial pulse tracing.
5. R–R′ interval: The interval between the R wave of one cardiac cycle to that of the next cycle.

These five observations were made on three groups of individuals:

a. Control group: Fifteen normal volunteers were observed at rest, and then following sufficient strenuous exercise to produce a definite tachycardia.
b. Group with pre-medication: Ten normal volunteers were observed at rest and following the routine pre-operative medication of Nembutal 92 mg., Demerol 100 mg., scopolamine 0.3 mg. orally. This medication was identical to that given to the group subjected to ether anesthesia as pre-medication. The time after administration at which the measurements were made was the same in this control group as in those given ether anesthesia.
c. Group anesthetized with di-ethyl ether: Ten subjects, normal except for inguinal hernia or varicose veins, were observed at rest. Pre-medication consisting of Nembutal 92 mg., Demerol 100 mg., scopolamine 0.3 mg. was given and, approximately one hour later, they were induced and anesthetized with ether. During surgery anesthesia was continued until Plane III and Plane IV were reached, at which time the tracings were repeated.

All results on each group of individuals were averaged and subjected to statistical analysis. The standard deviation σ was calculated according to the formula $\sigma = \pm\sqrt{\frac{\Sigma x^2}{(n-1)}}$ were x is the deviation of the observations from the mean, and n the number of observations.

The standard error of the mean, ϵ (M) indicating the limits between which the mean can be expected to be found, was calculated by the formula: $\epsilon\,(M) = \pm \frac{\sigma}{\sqrt{n}}$

The standard error of the difference between two means, M_1 and M_2, was calculated by the formula: $\epsilon\,(M_1 - M_2) = \pm\sqrt{\epsilon_1^2 + \epsilon_2^2}$

If the difference between two means was three times the standard error, or more, the difference was regarded as statistically significant.

Results. The results of the observations of the control group, with statistical analyses are presented in Table 1. The mean arithmetic averages for all individuals at rest were: Q-wave–1st tone, 0.059 second; 1st tone–2nd tone: 0.327 second; 1st tone—carotid pulse rise: 0.069 second; Q-wave—carotid pulse rise: 0.127 second. These figures were obtained when the R–R′ interval was 0.897 second.

Following exercise, the mean R–R′ interval of the control group was 0.474 second. The 1st–2nd tone duration was markedly shortened to 0.222 second with this tachycardia, and the remaining measurements showed significant reduction in each instance.

In analysis of the 10 individuals receiving pre-medication only, the mean values for each interval prior to drug administration were as follows: Q-wave –1st tone: 0.055 second; 1st tone—carotid pulse rise: 0.080 second; Q-wave –carotid pulse rise: 0.126 second; 1st tone—second tone: 0.35 second; R–R′ interval: 0.99 second. These control observations were compared to results obtained during the influence of the pre-medication which deviated most from the control. The cardiac rate slowed so that the mean R–R′ interval was 1.11 seconds. While the lengthening of the intervals occurred, the changes observed in all were not significant and no specific effect of the drugs was obtained.

During deep ether anesthesia, the mean R–R′ interval was shortened to 0.613 second; and at the same time,

TABLE 1.—TIME RELATIONSHIPS BETWEEN THE ONSET OF THE VENTRICULAR ELECTROCARDIOGRAM, OF THE FIRST HEART TONE, AND OF THE CAROTID ARTERIAL PULSE RISE AT REST AND DURING STRESS. STRESS WAS INDUCED BY STRENUOUS EXERCISE IN THE CONTROL GROUP, BY DEEP ETHER ANESTHESIA IN THE ANESTHETIZED GROUP.
(ALL VALUES EXPRESSED IN SECONDS)

	REST					STRESS				
Category	*Q–1st*	*1st–2nd*	*1st–Car*	*Q–Car*	*R–R′*	*Q–1st*	*1st–2nd*	*1st–Car*	*Q–Car*	*R–R′*
Control	056	319	069	125	882	048	222	045	093	474
						M_1	M_2	M_3	M_4	
S. D.	011	029	012	013		009	028	009	012	
E. M.	00294	0079	00321	00342		00241	00763	00252	00321	
Ether anesthesia	061	3386	069	130	919	059	264	061	120	613
	M_9	M_{10}	M_{11}	M_{12}		M_5	M_6	M_7	M_8	
S. D.	009	030	009	015		013	034	011	020	
E. M.	0031	0095	00299	0048		0041	0110	0035	0063	
E (M_1–M_5)						00475				
E (M_2–M_6)							0134			
E (M_3–M_7)								00419		
E (M_4–M_8)									0071	

the 1st–2nd tone interval decreased to 0.264 second. The remaining measurements, Q–1st tone, 1st tone–carotid rise, and Q-wave–carotid rise, were not significantly decreased from their control values. In no case did these observations during deep ether anesthesia differ from the control values by an amount equal to either two or three times the standard error of the difference between their mean values.

Discussion. Observations (Katz and Feil[14], and Wiggers[26]), utilizing arterial pulse wave records and simultaneous phonocardiograms have demonstrated that the duration of total systole and the ejection period is also shortened by the action of epinephrine, carbon dioxide, and the accelerator nerves while the isometric period is similarly but less consistently affected by such factors and is more variable.

Extension of this type of analysis to include the relationship between electrical and mechanical events of the cardiac cycle have been limited to a single heart rate and dealt largely with the interval between the onset of QRS wave and of the carotid or brachial arterial pressure rise. Previous observations on the mean duration of this interval (Q–carotid rise) in normal human beings have been reported variously as: 0.06 to 0.12 (Battro[1]), 0.111 second (Wolferth[27]), 0.120 (Castex[8]), and 0.139 second (Kossman[16]). The findings of the present study agree closely with these results, showing a mean value of 0.125 second when the R–R′ interval is 0.882 second. In addition, a definite shortening effect of the mean Q-wave–carotid pressure rise interval resulted from increased heart rate, for the mean Q–carotid pressure rise interval decreased to 0.093 second when the R–R′ interval became 0.474 second; the former interval shortened in each individual case and the mean decrease was highly significant statistically. Since this interval, uncorrected

for pulse wave velocity, is considered to give an indirect evaluation of the duration of the isometric contraction time of the left ventricle (Coblentz *et al.*[10]), the similar effect of cardiac rate on both intervals is to be expected and should be considered whenever analysis of the Q-wave–carotid pressure rise is made as in studies of asynchrony of ventricular contraction in bundle-branch block.

An analysis of the four variables whose sum compose this interval, described as the Q–E interval, and its significance was made by Katz, Landt and Bohning[15]. The first variable, a latent period between the onset of ventricular stimulation and the time when sufficient potential difference is developed to be detected by the electrocardiograph, was not considered in the present study. It has been shown by Nichol[24] that this variable is insignificant as long as only one electrocardiographic lead is used consistently, as in this present study, for measurements. A second variable is the time lag involved in transmitting the pulse from the ventricle to the point of registration: since the same site for carotid artery pulse wave was employed for recording at all times, and since the blood pressure was unchanged, this time lag was considered to be an invariant in the present observations. A third variable is the latent period between the onset of the QRS complex and the onset of the mechanical portion of systole, while the fourth is the true isometric contraction period. Only the last two of these variables have been considered, and their sum or this total interval between the beginning of QRS and the onset of carotid arterial pressure rise has been divided by Messer *et al.*[22] into an initial period of electrical activity and, following this, a period of mechanical activity. The initial period, the time elapsing between the onset of the QRS complex and the onset of the main vibrations of the first heart sound is a measure of the rapidity of the electrical spread of the depolarizing wave in the ventricular myocardium as well as the response of the myocardium to the wave. It has been studied at a single, fixed heart rate and mean values range from 0.02 second (Orias[25]) to 0.050 second (Mannheimer[19]); in the present study a mean duration of 0.056 second was obtained at an R–R′ interval of 0.882. Hence, again, a significant shortening effect resulted from an increased cardiac rate, the period decreasing to 0.048 second at an R–R′ interval of 0.474 second.

The second period, of mechanical activity, is expressed as the interval between the onset of the major vibrations of the first heart tone and the onset of the carotid arterial pulse rise. It is a measure of the rapidity of mechanical contraction of the ventricles. Assuming identical pulse wave transmission velocity at different cardiac rates, it was this second period which was responsible in major part for the effect of the change of cardiac rate on the duration of the interval between the onset of QRS and the carotid pulse rise or the indirect isometric contraction period of the left ventricle. When the rate of cardiac acceleration remained constant, the second period of mechanical activity was decreased markedly, from 0.069 second to 0.045 second. This difference of 0.024 second is approximately 75% of the total shortening observed in the indirect isometric period, the QRS–carotid pulse rise interval, as the cardiac rate increased.

This implies that the predominant effect of cardiac stimulation produced by exercise upon the isometric period of the left ventricle is to shorten the period largely by acceleration of the

second, or mechanical, phase, and, to a lesser degree, by acceleration of its electrical phase.

This type of analysis offers, furthermore, a sensitive method for the study of the cardiac effects of procedures, or drugs, even if the heart rate changes result. A study of general anesthetic agents and their cardiovascular actions were of special interest to the authors since anesthetic administration and surgery have made it difficult to apply other techniques for research. Although it has been asserted that heart function remains unimpaired during clinical anesthesia produced with di-ethyl ether (Beecher[2]), electrocardiographic changes have been reported frequently since their early observation by Kurtz[17] in 1936, and cardiac output has been shown to be decreased by Brewster and his co-workers[7]. When the methodology of the present study was applied to a group of young adults prior to, and during, Plane III and Plane IV anesthesia produced by di-ethyl ether, certain definite effects were attributable to the anesthesia. The effect of the pre-medication drugs employed was found to be negligible. Tachycardia was produced in the control group by exercise and, to a slightly less degree, in the other anesthetized group as shown by a 45% and 34% decrease, respectively, in the mean R–R′ intervals. This was accompanied, in both the control and anesthetized groups, by a shortening of the 1st–2nd tone interval which was roughly directly proportional to the total duration of the cardiac cycle. No specific effect was noted in this respect from ether anesthesia.

During deep ether anesthesia, the indirectly-measured isometric period of the left ventricle (Q-wave–carotid pulse rise interval) showed a negligible decrease from 0.130 to 0.120 second. Furthermore, in contrast to the effects observed during exercise-induced tachycardia, neither the electrical nor mechanical phase of this isometric period showed a significant decrease during the tachycardia associated with deep ether anesthesia. The electrical phase (Q-wave–1st tone interval) changed by only 0.002 second, from 0.061 to 0.059 second; the mechanical phase 1st tone–onset of carotid pulse rise) changed from 0.069 to 0.061 second. Thus, both components of the isometric period, as well as the period itself, occupied an increased percentage of the total cardiac cycle during anesthesia. Insofar as the tachycardia and shortened 1st–2nd tone interval produced by both exercise and ether anesthesia are mediated by sympathetic stimulation (Beecher[2]), changes produced in the proportion of the cardiac cycle occupied by these components may be attributed to the effects of deep ether anesthesia. It may be concluded from this data, therefore, that deep ether anesthesia produced a relative inhibition of both the electrical spread of the depolarizing wave in the ventricular myocardium and the response of the myocardium to this wave, as well as inhibition of the rapidity of mechanical contraction of the ventricle. These alterations may accompany the diminished contractile force of the heart, demonstrated by the use of resistance strain gauge arches, observed during ether anesthesia (Boniface, Brown and Kronen[6]).

Summary. 1. The temporal relationships, as recorded on the electrocardiogram, phonocardiogram, and carotid arterial pulse wave records were studied in human beings under conditions of changing cardiac rate and ether anesthesia. The intervals between the onset of the QRS complex and the onset of the first heart sound and of the carotid arterial pulse wave rise, between the first tone and the onset of the carotid arterial pulse wave rise

and the onset of the second tone were related to change in cardiac rate.

2. Cardiac acceleration produced consistent shortening of the indirectly measured isometric period of the left ventricle, due largely to shortening of its mechanical phase.

3. The results obtained during deep ether anesthesia were considered to indicate that this type of anesthesia produced inhibition of rapidity of both the electrical and the mechanical events within the myocardium.

4. The technique employed appeared to offer a sensitive means to study certain dynamic aspects of cardiac action. It appeared to have special value in the evaluation of procedures or drugs when other means of study are not feasible.

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(Interlingua on page 694)

TREATMENT OF ANGINA PECTORIS WITH DISODIUM ETHYLENE DIAMINE TETRAACETIC ACID*†

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A practicable problem is existing atherosclerosis and how to increase needed blood supply to endangered tissues or vital organs. When help is sought the question of diet has become purely academic. Also it is certain that people who can afford high fat diets will not eat less desirable foods even if they might prolong their lives.

There is no readily available test for diagnosing atherosclerosis or anticipating its fatal complications while its causes remain obscure. It is known to have many facets such as lipids, proteins and carbohydrates and to these can be added minerals with emphasis on calcium. For calcium is integrated with the cholesterol in an atheroma and thereby becomes an active participant in a living pathological structure. Atheromas grow in the coronary arteries and produce, as one of their effects, the clinical syndrome of angina pectoris. The treatment of this common fatal disease has been defeatist or palliative.

Our purpose was to apply the principles of chelation to the bound or living calcium and possible other unknown minerals, with the belief that this would disintegrate the organic atheromatous matrix and allay the symptoms of angina pectoris.

The difficulties of diagnosing angina pectoris and evaluating its therapy were carefully considered. The selection of patients was based on special characteristics of their disease. In one group the typical chest pain was of recent onset but had increased in frequency and severity. Another group had histories and electrocardiographic evidence of old myocardial infarctions, followed at various time intervals by angina pectoris of increasing severity. Several patients also had peripheral vascular disease and intermittent claudication. The disease was confirmed independently by two or more physicians. We did not use the two-step exercise test which is not without danger and has the fault of patient and doctor interpretation. As the diagnosis of angina pectoris is determined by the clinical history, so must the evaluation of therapy be decided by the absence of symptoms under increasing physical activity. The electrocardiograms and serum stability tests were used in clinical appraisal.

We weighed other possible explanations for the improvement in these patients. Only 4 of the 20 patients were hospitalized for periods of 2 to 3 weeks and they were ambulatory except for the 2 to 4 hours each day they re-

*The EDTA used in this investigation was provided by the Sherman Laboratories, Detroit, Michigan.

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ceived the infusion. The others were treated as office patients and continued their normal activities with some working. We do not believe that rest under these conditions could have been an influencing factor. A placebo action seemed improbable for several reasons. There was slight if any clinical improvement until after the discomfort of 20, and with a few, 30 infusions. A patient's progress was based on measured physical activity rather than appraisal of subjective symptoms. The improvement gained has been retained and expanded in all, and a few for as long as 2 years. The results have been uniformly good.

Method. A solution of 5 gm. of the disodium salt of ethylene diamine tetraacetic acid in 500 ml. of 5% glucose or normal saline was given intravenously. The intravenous drip was regulated to require 2.5 to 4 hours for the total infusion. We ultimately found it most satisfactory to give 5 gm. a day for 5 days and omit it for 2 days. Occasionally 5 gm. given every other day was better tolerated but 10 to 15 infusions in a series and stopping it for 1 or 2 weeks gave the best results. The fewest number of infusions given to a patient was 15 and the most 60 with an average of about 35. To small people we gave 3 or 4 gm. of EDTA in the daily infusion. We have continued with short series of 5 daily infusions of EDTA every 6 months.

THE IN VIVO DISSOLUTION OF METASTATIC CALCIUM. The metastatic calcium of renal calcinosis can be safely removed by prolonged intravenous infusion of ethylene diamine tetraacetic acid or EDTA (Clarke, Clarke and Mosher[7]). It is equally important that the *in vivo* action of EDTA persists long after its use.

One of our patients had a large foul smelling necrotic ulcer on the right side of his neck which had developed following a thyroid operation performed 7 years before. The removed thyroid tissue was diagnosed malignant and he had intensive deep radiologic therapy. In the treated area extensive deposits of metastatic calcium formed throughout the deep neck tissues extending from the base of the skull to below the clavicle. He was given daily intravenous infusions of 5 gm. of disodium EDTA in series of 15 to a total of 600 gm. The neck ulcer healed in at the base and laterally, its walls became epithelialized, the foul odor was eliminated and he regained normal mobility of the neck. Much metastatic calcium was removed along with the considerable healing of the ulcer.

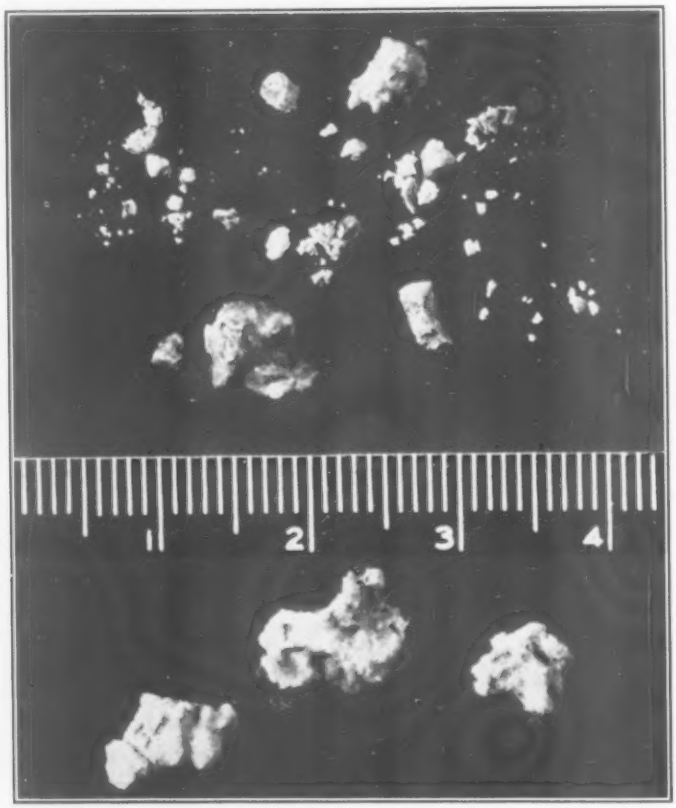
During the year that followed disodium EDTA therapy the patient with renal calcinosis continued to pass large amounts of sand and stones in his urine like the few pictured in 1*A* and for 10 months the patient with the healing neck ulcer extruded through a sinus tract many small to large calcified plaques as in Fig. 1*B* which were eroded at their outer surfaces (Brant[18]). It is not known how long this continuing action persists.

The *in vivo* dissolution of metastatic calcium occurs from the endocardial or intimal surface of the cardiovascular system. A patient with rheumatic heart disease for a year had been sleeping elevated on several pillows or in a chair and entered the hospital through the emergency ward with acute dyspnea and coughing up blood. She had choking sensation and pain with severe tightness in the upper chest and throat. Similar spells of increasing severity occurred during the previous 10 months.

A solution of 5 gm. of disodium EDTA in 500 ml. of saline was given intravenously and repeated for 12 days. After receiving 45 gm. she was awakened by a short intense pain in the mid-left chest anteriorly which was repeated and had a severe tearing quality. It was immediately possible for her to breath normally and sleep without a pillow. She resumed almost

normal activities and remained free of symptoms without using digitalis. The sudden severe chest pain may have occurred with the tearing apart of the weakened commissural adhesions of the mitral valves, and her immediate symptoms were confirmed by fluoroscopy. With the fluoroscopic field narrowed down the ovoid valvular calcification moved up and down with the movement of the heart and also when the breath was held, and was not seen after EDTA

A



B

Fig. 1A.—Calcified material passed from kidneys one year after EDTA therapy. *B.* Material from neck sinus 10 months after EDTA therapy.

tomatic relief resembles a successful surgical commissurotomy.

The roentgenograms taken just prior to treatment with disodium EDTA showed a calcified mitral ring which was not visible in the roentgenograms taken 4 months later. The findings

therapy. From this evinced *in vivo* ability of disodium EDTA to remove metastatic calcium and especially from the endocardial or intimal surface of the heart it seemed logical for it to do the same from the intimal portion of arteries. We report 20 pa-

tients who had carefully confirmed, seriously progressive, angina pectoris.

PATIENTS WITH ANGINA PECTORIS TREATED WITH DISODIUM EDTA. **Case Reports.** CASE 1. W.L., a 50-year-old factory worker had angina pectoris in 1949 and in February, 1954, had increased difficulty requiring 10 to 15 nitroglycerin tablets a day. Walking half a city block produced the pain.

In February disodium EDTA therapy, 5 gm. a day for 15 days was initiated. A month later there was slight if any symptomatic relief. In March, 5 gm. of disodium EDTA was given daily for 15 days. After 7 infusions he was walking about the hospital and using only one nitroglycerin tablet a day. He continued to improve and by mid April was walking half a mile without angina pectoris. A month later he walked a mile without discomfort. From May, 1954, to November, 1955, he worked regularly and walked a mile or farther without symptoms.

CASE 2. F.M., a 60-year-old factory worker had an anteroseptal myocardial infarction in late January, 1954, and was hospitalized. He had frequent attacks of substernal pain daily brought on by slight exertion. Five days after his coronary occlusion he was given the first of 15 daily infusions of 5 gm. of disodium EDTA. His attacks of angina pectoris persisted with moderate effort. In March he received 15 daily infusions of 5 gm. of disodium EDTA. In early April he was walking 4 blocks without discomfort and his exercise tolerance improved so that he returned to work in late April. In June he was living a normal life and even lifting heavy metal objects without symptoms. He had remained free of angina pectoris when seen in November, 1955.

CASE 3. W.McL., a 68-year-old mechanic had his first attack of angina pectoris in 1947. His activities were not limited until early in 1953. A diseased gallbladder was removed in November, 1953, after which he improved until January, 1954, when the angina pectoris increased rapidly. In February, 1954, he received 15 daily infusions of 5 gm. of disodium EDTA without benefit. A few days later he had a convulsion, lost consciousness and died within a few hours.

At necropsy, his aorta showed extensive atheromatosis. In some zones the atheromatous material containing lipid was diminished with some necrosis, degeneration of the supporting stroma and slight polymorphonuclear infiltration. The coronary artery sections showed intense medial sclerosis with calcification and general narrowing of the lumen but no atheroma. The kidneys showed tubular nephritis and mild glomerulitis that was considered to be terminal. There was no vacuolization of kidney cells. The coronary pathology was medial sclerosis with no occlusion or atheroma. Examination of the head was not permitted but we suspected that he died from a calcium embolus that had been freed from a large arterial plaque.

CASE 4. T.S., a 57-year-old factory superintendent had his first attack of angina pectoris in 1951. In 1952 he developed intermittent claudication for which a sympathectomy was advised and refused. In November, 1953, the angina pectoris and intermittent claudication increased so that an attack could be induced by walking 100 feet. In March, 1954, he was given 20 daily infusions of 5 gm. of disodium EDTA. In May he resumed work and stated "before I could hardly lift a shovel without causing pain, now I am shoveling dirt with no pain." He continued his normal activities and without leg or chest pain until December, 1954, when there was a return of mild angina pectoris. The following February he had severe substernal pain and his electrocardiogram showed anterior myocardial ischemia. His symptomatic recovery was rapid and his electrocardiogram was normal within 2 weeks. He had remained free of symptoms when seen in November, 1955, and had been doing his normal work. The acute attack of chest pain, occurring after the many pain-free months which followed disodium EDTA therapy with the rapid symptomatic and electrocardiographic recovery, could conceivably have been embolism from a honeycombed loosened calcium plaque.

CASE 5. J.K., a 73-year-old office building superintendent had intermittent claudication for several months before his first attack of angina pectoris in December, 1954. By January a walk of half a block would produce an attack of angina pectoris. In January and March, 1955, he received a series of 15 daily infusions of 5 gm. of disodium EDTA which was given in groups of 5 and omitted for 2 days between. In February he walked 2 blocks against a cold wind without pain. He continued to improve so that by April he was normally active and walking any required distance without having chest or leg pain. In November, 1955, he had continued free of both intermittent claudication and angina pectoris under normal physical activities.

CASE 6. H.V., a 55-year-old executive was supposed to have had a coronary occlusion in 1946. He had mild attacks of angina pectoris in June, 1952, which occurred with exertion

after eating breakfast. He continued to have occasional attacks of chest pain until September, 1953, when they increased so that by July, 1954, he was using 8 to 10 nitroglycerin tablets daily and walking across a room caused angina pectoris.

In July he received 29 daily infusions of disodium EDTA given for 5 days and stopped for 2 days between. Since mid-September he had been normally active, walked up to 10 blocks without angina pectoris and discontinued the use of nitroglycerin tablets. In October, 1955, he had continued with his regular work and had only an occasional slight substernal ache if he exerted unusually following a heavy meal. He had regained his normal strength, vitality and interest in his work.

CASE 7. J.O., a 59-year-old office worker had a myocardial infarction in 1951. Angina pectoris appeared in February, 1953, and progressed so that he had to stop work in September, 1953. In January and March, 1954, he received a series of 15 daily infusions of 5 gm. of disodium EDTA. By the end of February he was walking 6 blocks without angina pectoris. In May he had 8 daily infusions of 5 gm. of disodium EDTA and by July he was free of angina pectoris even when doing heavy work. He had remained free of angina pectoris when last seen in November, 1955.

CASE 8. E.B., a 54-year-old toolmaker had angina pectoris in September, 1952, which increased so that by November, 1953, he could not walk 100 feet without the chest pain. In November, 1953, he was given 14 daily infusions of 5 gm. of disodium EDTA. One month later he had noticed slight relief.

A series of 14 infusions of disodium EDTA was given in January, 1954, and in February he was walking several blocks in cold weather without angina pectoris. A series of 15 infusions was given in February and by late March he was walking 3 miles without symptoms. He continued free of angina pectoris even after walks of several miles. His last disodium EDTA was given in June at his request. He had continued free of angina pectoris and was moving to another city.

CASE 9. A.K., a 56-year-old housewife had angina pectoris in late January, 1954. The attack was severe and in the following 6 weeks occurred with decreasing exertion. In March she was given 15 daily infusions of 5 gm. of disodium EDTA. In April she was walking 3 blocks without angina pectoris. In July, 1954, she was doing her regular housework without pain and had remained symptom free when seen in October, 1955.

CASE 10. E.O'D., a 59-year-old night watchman. In 1946 he had severe substernal pain following exertion that lasted 2 hours before being relieved by narcotics. In September, 1954, he had angina pectoris which increased in frequency and severity until he was forced to stop work in December. He was then given 21 daily infusions of 5 gm. of disodium EDTA. By the end of January, 1955, he was walking 4 blocks without angina pectoris. A series of 5 daily infusions was given in February after which he returned to work. From March to November he had worked and walked a mile or more without angina pectoris.

CASE 11. C.S., a man, aged 59, had severe substernal pain in September, 1952, which lasted for half an hour. He worked the following day and felt well until August, 1955, when following exertion he had severe substernal pain which radiated into his lower jaw. The pain lasted for half an hour or until relieved by morphine. He had a similar attack of substernal pain 5 days later and they continued to occur with slight exertion. The pain was relieved by nitroglycerin. He had not worked the 5 days before he was seen. In late August, 1955, he received 10 daily intravenous infusions of 5 gm. disodium EDTA in 500 ml. of saline solution. A few weeks later he was walking 2 blocks without angina pectoris and not using nitroglycerin tablets. In October he received 15 daily infusions of disodium EDTA given for 5 days and stopped for 2 days between. In November he was walking 8 blocks without angina pectoris.

CASE 12. S.V., a woman, aged 57, had gained weight rapidly and in June, 1952, had an attack of substernal pain brought on by exertion which radiated to the neck and left arm, and was relieved by rest. Her electrocardiogram was normal. The attacks of substernal pain gradually occurred with less exertion and increasing severity until August, 1954, when they limited her activities. In July, 1955, the angina pectoris became more severe. She was hospitalized and given 15 daily infusions of 5 gm. of disodium EDTA. She was distressed by the intravenous infusions, complained bitterly and had difficulty in completing the schedule. A month later she was walking four blocks, doing part of her work without angina pectoris but refused further treatment.

CASE 13. E.K., a man, aged 46, had angina pectoris in November, 1953. Attacks were infrequent up to November, 1954, when following strenuous exertion he had a severe

attack. Since then the pain had occurred with less and less exertion and been worse if he exerted following eating. He could walk slowly on level ground for several blocks but light yard work would cause angina pectoris. During the 3 weeks before he was seen he had had several attacks of severe nocturnal dyspnea. The disodium EDTA was given in June and July, 1955. Each course consisted of 15 daily infusions of 5 gm. of disodium EDTA given in groups of 5 and stopping for 2 days between. After the first course of 15 infusions he worked in his yard and had but one attack of substernal tightness and dyspnea. A second series of 15 daily infusions of disodium EDTA was completed in August. In late August he resumed his regular occupation and was doing considerable work around his home with only one mild attack of substernal pain and another when he overexerted following a large dinner. A course of 15 daily infusions of 5 gm. of disodium EDTA was given in August, and in September he did heavier work about his home without angina pectoris. In October he resumed his full work load and did heavy work about his home without fatigue or angina pectoris. In November he was free of angina pectoris under every normal activity.

CASE 14. D.S., a man, aged 59, became unusually nervous in October, 1954, and had spells of rapid heart action that lasted up to one hour. In January, 1955, walking caused pain in the calf muscles and substernal pain which were relieved by rest. They increased so that walking one block would make him stop and rest. Two weeks before he was seen he had an attack of weakness, dizziness and feeling of faintness. Similar attacks recurred every few days with rapid beating of the heart. Following one attack he was unable to speak clearly or co-ordinate his words although knowing what he wanted to say. He started to tire easily. His electrocardiogram taken in April, 1955, showed myocardial damage with the T waves inverted in leads I and V5, V6, and AVL. His electrocardiograms did not change during our period of observation. He was given a course of 13 daily infusions in June and in August, 11 daily infusions of 5 gm. of disodium EDTA in series of 5 and omitted for 2 days between. In July he had some relief from his angina pectoris having but one mild attack while playing golf. In August he was walking normally about the plant where he worked without angina pectoris or leg pain. He was relieved of the attacks of rapid pounding heart action. He lost his former feeling of mental depression and the slight difficulty he had had in cerebration. He was able to walk at least 8 blocks without angina pectoris or intermittent claudication. In September he remained free of angina pectoris and considered his ability to walk and work as normal. In October he increased his work responsibilities and was handling them with only slight nervousness, but no chest or leg pains although walking as far as 12 blocks.

CASE 15. L.S., a man, aged 62, in February, 1955, had severe substernal pain following heavy exertion which was relieved by rest. The substernal pain recurred with less exertion or when emotionally upset and was relieved by rest. In May he had to stop work. His blood pressure and heart size were normal but he had atrial fibrillation with a ventricular rate of 80. In May he received 12 daily infusions of disodium EDTA given in series of 5 and omitted for 2 days between. The therapy was stopped because of diarrhea but he had been relieved of stiffness and pain in his legs and felt stronger. There was no change in the angina pectoris. He received 10 daily intravenous infusions of 5 gm. disodium EDTA in June, given in series of 5 and omitted for 2 days between. After 6 infusions he was walking 8 blocks without angina pectoris. In July his improvement had continued so that he started to work at the factory and was doing work around his home with only a rare and slight substernal sensation which did not require rest. In August he was symptom free although lifting weights of up to 100 pounds and walking and climbing stairs which previously caused angina pectoris. In October the atrial fibrillation was converted to normal sinus rhythm by quinidine sulfate and the ventricular rate was 72. His blood pressure was normal and no heart murmurs were heard. His first electrocardiagram taken in May, 1955, had an RS complex in leads V1, V2, V3 and V4 with inversion of the T waves in these leads and also in V5. In the electrocardiogram taken in July the T waves in the V leads were upright, and in that of October the T waves were upright in all limb leads. The electrocardiogram in November showed sinus rhythm with normal upright T waves in all leads except AVF.

CASE 16. J.O., a man, aged 55, in February, 1955, had substernal pain radiating into the neck which was caused by exertion and relieved by rest. An electrocardiogram taken in March showed flat T waves in lead I, inverted T waves in V6 and frequent ventricular extrasystoles. The electrocardiograms taken in May showed coved and inverted T waves in lead I with end inversion of the T waves in V4, and coved inverted T waves

in V5, V6 and in AVL. In June he had 15 daily intravenous infusions of 5 gm. of disodium EDTA given daily for 5 days and stopped for 2 days between. Two weeks after therapy he walked a mile without angina pectoris but continued to be apprehensive and when emotionally disturbed he would have a tight painful sensation in the region of the suprasternal notch with a sense of choking and dyspnea. A course of 15 daily infusions of 5 gm. disodium EDTA was given in August. In September he was free of angina pectoris under normal activity although remaining apprehensive. He was given 15 daily infusions of 5 gm. of disodium EDTA in September. By the end of September he was walking 2 miles without angina pectoris. In October he was working daily and walking several miles without angina pectoris and his heart rhythm was normal. From March to May, 1955, his electrocardiograms had showed signs of increasing myocardial ischemia. These signs had decreased in June when the disodium EDTA therapy was started. The persistent and frequent ventricular extrasystoles which were present prior to therapy were absent afterwards.

CASE 17. L.K., a woman, aged 69, in January, 1954, had pain in her left hip, thigh and calf muscles, and also dyspnea and heart palpitation brought on by exertion with all symptoms relieved by rest. The leg pains increased so that walking less than one block would require rest. A pulse could not be felt in either foot and the left leg was cooler to touch than the right. For several months the leg pains had been alleviated by Priscoline. In August, 1955, she had substernal pain brought on by exertion and relieved by rest. By September the substernal pain was radiating upward into the jaw and occurring with slight exertion. In October and November she was given a series of 15 daily intravenous infusions of 5 gm. of disodium EDTA in series of 5 and omitted for 2 days between. Her electrocardiogram taken in January, 1955, had deep Q waves and coved inverted T waves in lead 3 that suggested a previous posterior coronary occlusion. Her electrocardiogram taken just prior to therapy showed increasing myocardial ischemia with inversion of the T waves in leads 2 and 3, and depression of the ST segment in lead 1 with depression of the RT and inversion of the T waves in V6 and AVF. In November and December after therapy the electrocardiograms were normal and she was walking 6 blocks without chest or leg pain.

CASE 18. P.M., a man, aged 52, in 1951 had dyspnea with exertion for 3 weeks and then substernal pain which was relieved by rest. In one attack the pain radiated into his left arm and he was nauseated. He was kept in bed for 2 weeks. Later the chest pain occurred in bed and he would sit up for relief. He returned to work but walking as little as 50 yards would cause angina pectoris. His heart size was normal and blood pressure was 115/72. In April, 1955, he received 14 daily intravenous infusions of 5 gm. of disodium EDTA in series of 5 and omitted for 2 days between. Two weeks later the frequency and severity of his angina pectoris were less but walking faster than usual for two blocks would bring on an attack. He had 15 daily intravenous infusions of disodium EDTA in May. By the end of May he was walking 5 blocks slowly without angina pectoris unless it was following a meal. In June he had 15 daily intravenous infusions of disodium EDTA. In July he was walking at his normal pace for 5 blocks without angina pectoris. In October he was doing his regular work, walking fast and for any required distance, even as far as 2 miles without angina pectoris. His first electrocardiogram, taken in March, 1955, had deeply inverted pointed T waves in lead 3 with coved and inverted T waves in lead AVF. His electrocardiogram in May had Q waves in lead 3 with the T waves inverted but the T wave in lead AVF was flat to slightly elevated. In July the Q waves in lead 3 were of less amplitude and the T waves in leads 3 and AVF were normally upright. The same improvement continued in his electrocardiogram of September.

CASE 19. C.H., a man, aged 59, had a coronary occlusion in June, 1954, and was hospitalized for 6 weeks. He continued to have angina pectoris and in July, 1955, a walk of one block would produce an attack. The chest pain occurred with less exertion if he walked after eating a meal. In August he received 15 daily intravenous infusions of 5 gm. of disodium EDTA in series of 5 and omitted for 2 days between. After he had received 9 infusions he was relieved for the first time since January of the pain of bursitis in his right shoulder. He had had without relief local deep Roentgen-ray therapy and injections of hydrocortone. There was little change in the angina pectoris. A series of 15 daily infusions of disodium EDTA was given in September. In October he was walking 8 blocks and climbing stairs without angina pectoris. His strength improved as well as a general feeling of well being. His electrocardiograms taken in July, September, and October, 1955, showed inverted T waves in leads 2 and 3, V6 and AVF. This pattern

did not change during or after his treatment with disodium EDTA.

CASE 20. F.S., a man, aged 51, a clergyman, in March, 1955, had a coronary occlusion. The chest pain recurred with slight exertion but was relieved by rest or nitroglycerin. In September a severe attack persisted for several hours and radiated into the left arm. The attacks continued to occur with slight exertion, radiating into the neck and left arm until he had to stop work. Walking 200 feet would cause angina pectoris. Starting in September he received 28 daily infusions of 5 gm. of disodium EDTA in series of 5 and omitted for 2 days between. By mid-October he was free of angina pectoris while walking about the hospital corridors and climbing a flight of stairs. He was able to increase his physical activities and up to mid-December remained free of symptoms while performing his religious duties and walking as far as ten blocks. His electrocardiograms remained abnormal throughout the period of observation.

ELECTROCARDIOGRAMS. In occlusive coronary artery disease the changes in serial electrocardiograms are most significant. In uncomplicated angina pectoris the electrocardiogram is frequently normal or shows only the signs of transient myocardial ischemia. One cannot always be sure whether an abnormal electrocardiographic pattern is the result of ischemia, the residual of an earlier infarction, or both. Only rarely can electrocardiograms be correlated with treatment. In Fig. 2 are the before and after therapy electrocardiograms of 2 representative patients that show diminishing myocardial ischemia. In the patient, H.V., a pattern of T wave inversion in chest and limb leads had persisted for 2 years before therapy and been associated with angina pectoris. This man was examined in 1952 at the Mayo Clinic where they thought his electrocardiograms and clinical history indicated one and perhaps two earlier myocardial infarctions. The same abnormal electrocardiographic pattern was present in July, 1954, when disodium EDTA therapy was started and his angina pectoris was most severe. Following therapy he was almost completely relieved of angina pectoris and his electrocardiogram assumed a normal pattern. The electrocardiographic abnormalities had been due to myocardial ischemia. The patients E.O'D., L.K., P.M., and E.B., showed similar reversal of ischemic patterns after disodium EDTA therapy.

The patient, L. S., had atrial fibrillation. His serial electrocardiograms during EDTA therapy showed decreasing myocardial ischemia and after the restoration of sinus rhythm had only inversion of the T waves in lead AVF. He was then doing heavy physical work and was free of angina pectoris.

Of these 20 patients, 14 showed definite and 3 suggestive electrocardiographic evidence of myocardial damage or ischemia. In 6 patients abnormal electrocardiograms reverted to essentially normal patterns during or following disodium EDTA therapy. In 7 patients (E.K., F.S., W.L., G.O., D.S., C.H., and F.M.) there was a history of myocardial infarction and, while their angina pectoris was allayed, their electrocardiograms changed little if any during or after therapy.

All patients had been examined and serial electrocardiograms taken over periods of 2 months to 2 years before their disodium EDTA therapy was started. Their electrocardiograms were mostly in a state of fixed or progressively increasing abnormality. The reversal to normal in almost 50% of those without a history of myocardial infarction but with signs of myocardial damage in their resting electrocardiograms implies an action by disodium EDTA in improving myocardial circulation.

SERUM STABILITY. The colloidal stability of blood serum as measured by the time required for the surface tension to reach a fixed value in dynes is a laboratory observation which is altered by certain diseases.

The capillary height method of determining surface tension has been used in physical chemistry for many years. Its application to biological fluids is new and required the development of new techniques and standards. The details for this new test for atherosclerosis are embodied in a doctoral thesis submitted in September, 1955, to Wayne University by Herbert W.

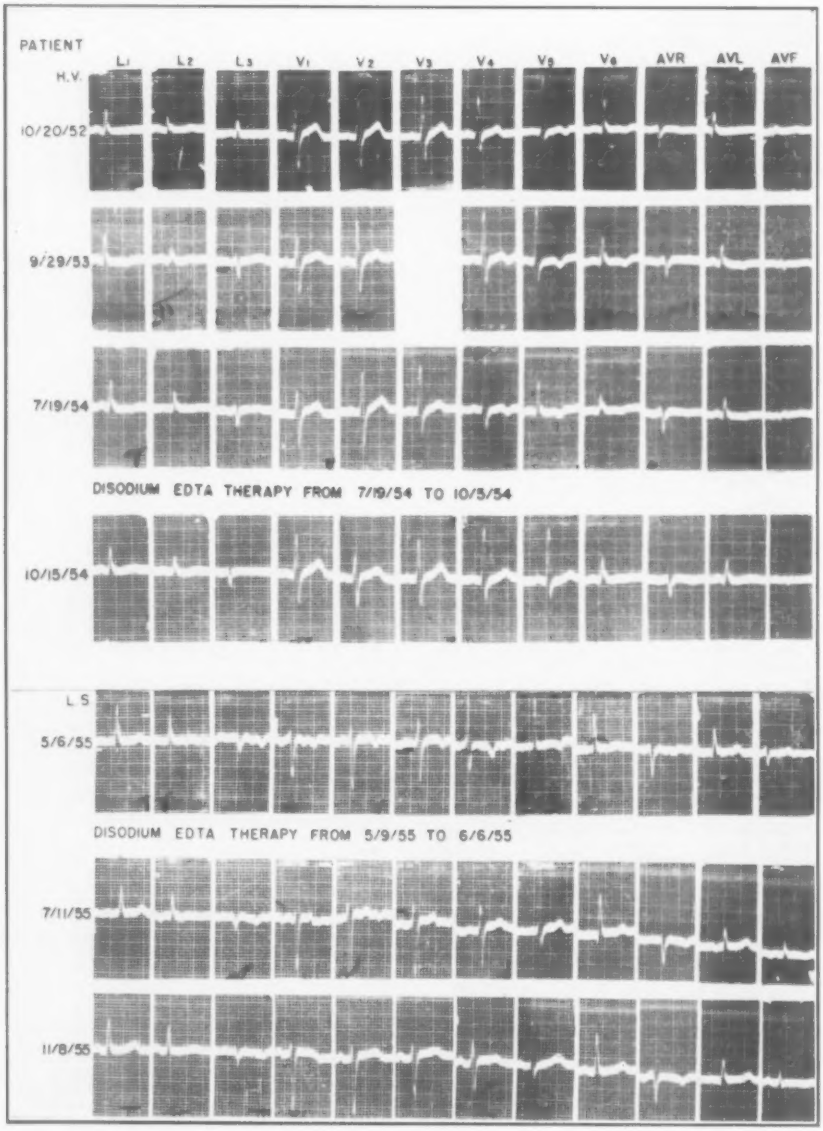


Fig. 2.—The 7 records reproduced above are the before and after electrocardiograms of 2 representative patients treated with EDTA in whom there was reversal toward normal that paralleled symptomatic improvement.

McCormick. The thesis is titled "The Surface Tension of Blood Serum in a Study on Atherosclerosis."

The serum stability is expressed in hours or the time required to reach a surface tension of 52 dynes per centimeter. The average normal value is 4.07 hours and average atherosclerotic value 3.19 hours. The greater the hours the greater the stability of the serum colloids. The surface tension of serum will vary with time in a reproducible manner. This phenomenon may be considered as an aging effect and attributable either to redistribution of electric charges or changes in hydration of the organic colloids involved. The rate at which this change occurs is inversely proportional to the stability of the colloids. We have obtained serum stability studies in 6 patients who had atherosclerosis and angina pectoris.

TABLE 1.—SERUM STABILITY IN HOURS OF PATIENTS WITH ANGINA PECTORIS BEFORE AND AFTER DISODIUM EDTA THERAPY. NORMAL AVERAGE 4.07 HOURS—ATHEROSCLEROTIC AVERAGE 3.19 HOURS.

Patient	*Prior to EDTA*	*After 75 gm. of EDTA*	*After 150 gm. of EDTA*	*After 225 gm. of EDTA*
C. H.	1.30	4.60	3.50	
P. M.	3.05	5.47		
D. S.	2.58	2.60	3.50	3.45
L. S.	2.46	3.43	3.75	3.90
W. L.	2.05	2.95	2.43	2.47
F. S.	2.00	..	1.95	..

Although limited in number the uniform abnormality of all sera prior to therapy with restoration toward normal values through the medium of disodium EDTA therapy makes these records significant. There is a large variation in response as to time and drug requirement. It is another objective confirmation of diagnostic accuracy and parallels elapsed time and observed clinical improvement.

TOXIC OR OTHER REACTIONS. From our experience of more than 4000 infusions of EDTA we found mild gastrointestinal symptoms common. Patients have nausea or diarrhea and occasionally severe epigastric pain, but do not vomit. Most of them maintain their appetite and rarely is it necessary to stop therapy. They complain of a burning sensation above the site of the intravenous needle which occurs particularly when the small hand veins are used, but it never required stopping the infusion. If the infusion was given rapidly some noticed a feeling of numbness around the mouth with giddiness and drowsiness. These symptoms disappear rapidly when the rate of intravenous flow is slowed. The incidence of gastrointestinal symptoms was reduced by giving 25 to 75 mg. of pyridoxine daily. Our experience in Case 3, who died suddenly following a convulsion, and in Case 4 who after a long period of freedom from angina pectoris had a sudden attack of myocardial ischemia from which he rapidly recovered, and similar experiences in other treated patients as yet not reported, raises a point of danger with this therapy. All such experiences suggest calcium embolism. In another patient (Boyle[17]) treated for calcified mitral stenosis, there was striking clinical improvement following disodium EDTA therapy but later sudden death from a cerebral accident. The necropsy disclosed multiple areas of embolism that originated from the honeycombed friable residual calcium on the mitral valve. Such experiences

with the calcium dissolving action of disodium EDTA speak for caution where large metastatic calcium areas involve the internal wall of the heart or large or vital arteries. This danger can be minimized by more days between infusions and longer rest periods. The hazard is minimal compared to that of occluding artery disease.

Discussion. It is evident that atherosclerosis which requires years for critical development, can only be alleviated and certainly not controlled within the brief periods of therapy reported.

The existence of calcium in atheromatous plaques has long been known but its more intimate relationship to precipitated cholesterol is becoming recognized (Faber and Lund[9], Miller *et al.*[14], Pareira *et al.*[16], and Uhl *et al.*[22]). When it was found that EDTA safely removed metastatic calcium from the human it could be expected to have an effect on atheromatous plaques. How this effect in the human body is produced or whether and how plaques are removed must await future study. A way is open that must be substantiated by time and the independent results of many competent investigators.

Although defects in lipid and cholesterol metabolism are of great importance in atherosclerosis, other factors must be involved. Mineral metabolism and in particular that of the alkaline earth metals is one such factor. The mineral change in the arterial wall parallels changes in organic composition. Both calcium and magnesium increase in the aortic albuminoid fraction and in the elastic fraction with increasing age and atherosclerosis and almost all of the mineral is deposited in an inorganic form (Miller, Hirschman and Kraemer[14]). Pareira, Handler and Blumenthal[16] have shown in amputated limbs that there is a distinct correlation between elastic-tissue calcium changes and the incidence and severity of atheromatous plaque formation. Analyses of human diabetic aortas with atherosclerosis showed an increase in the content of calcium and cholesterol which could be correlated with increasing age and hypertension (Faber and Lund[9]). A study of atheromatous aortas of rabbits showed a higher calcium and magnesium content and suggested a possible interrelation of cholesterol calcium and magnesium metabolism (Uhl *et al.*[22]). The inorganic and organic phases of atherosclerosis may be of equal importance and both may occur simultaneously rather than in sequence.

A probable sequence of events in atherosclerosis consists of reparative processes which go awry because of changes in the mucoid ground substance. This material with its content of highly polar polysaccharides and chondroitin sulfate is capable of fixing large quantities of calcium and cholesterol. Its affinity for calcium is well-known since calcium chloride solution is a standard extractant for removing chondroitin sulfate from tissue. There may be some special property of the polyuronides in regard to cholesterol, and a relationship between the presence of chondroitin sulfates in metachromatic tissue and the deposition of cholesterol. Metachromatic tissue is present in the intima and luminal part of the media of the human aorta and is always found in locations where cholesterol deposits are typically located. The polyuronides are probably bound more firmly to protein than is lipid material causing a displacement of lipid from lipoprotein and its consequent "dumping off" in metachromatic tissue (Faber[8]). A reduction in the stability of the serum cholesterol-protein complex could be of importance in the exchange process outlined here (Okunev[15]).

Calcium could be displaced from serum transudates by a similar mechanism. That colloidal forces play a part is indicated by the fact that calcium is held by both bone, mucopolysaccharides and serum proteins in a sort of ion exchange reaction. In this regard, Bauer, Marble and Bennett[1] report that when calcium is first deposited it does not necessarily have to be accompanied by phosphorus. This was concluded from balance studies rather than by direct tissue examination. Apparently, however, phosphate begins to be deposited soon after and the calcified area takes on a Ca/P ratio much like that of normal bone (Bauer *et al.*[1], Buck[4], and Key[11]). The resemblance to bone goes deeper than this in that pathological calcium deposits and in particular arterial plaques not only contain citric acid in proportions similar to that in bone (Buffa and Colajanni[5]) but also contain a mucopolysaccharide matrix like that of bone (Rubin and Howard[20]).

One of the factors in the calcification of cartilage is the content of chondroitin sulfate and the degree of polymerization of chondroitin (Loewi[13]). Presumably the number of side chains available for acceptance of calcium ions has been increased. The cartilage binds calcium by an ion-exchange process and phosphate is taken up only by cartilage containing appreciable amounts of calcium (Boyd and Neuman[3]). Once again, the binding capacity was correlated closely with the chondroitin sulfate content. In extensive studies Sobel and Hanok[21] concluded that sulfate-containing mucopolysaccharides appear whenever calcification takes place. The combination of calcium with some constituent of the ossifying matrix is an essential preliminary step in the mineralization process. Chondroitin sulfate may be the target of activating and reactivating ions. Studies of the calcification process in the presence of Ca_{45} (Lacroix[12]) and S_{35} (Belanger[2]) indicate that calcium and sulfur are laid down together and that a sulfur-containing compound, possibly sulfated mucopolysaccharide, is involved. Although certain other mineral elements such as iron (Bunting[6]) may be involved in these processes further discussion is beyond the scope of this paper.

Although decholesterolizing agents have been used in the therapy of atherosclerosis, this form of attack has not met with much success (Pomeranze and Chessin[19]). The next obvious therapeutic attack on this disease was the removal of metastatic calcification in areas of arterial wall degeneration. It should be emphasized that metastatic calcification is not the only process of importance in this disease. Undoubtedly alterations in lipid metabolism, enzyme chemistry, trace elements and serum "stability," to mention a few, may be of equal or greater importance but the attack upon metastatic calcification appeared to offer a reasonable prospect of success in the therapy of atherosclerosis. The infusion of calcium in dogs produced a prompt decline of up to 39% in blood cholesterol (Goebel[10]). This suggests a chemical clearing action by calcium on cholesterol in transport. The manner of such action is not clear but it shows an interrelationship.

Summary. 1. The treatment of coronary artery atheromatosis with its commonly fatal syndrome of angina pectoris has been approached through the calcium cholesterol integration in the matrix.

2. The chelating agent ethylene diamine tetraacetic acid was used because of its ability to remove metastatic calcium and especially from the endocardial surface of the human heart.

3. It has been found that EDTA action devitalizes living metastatic calcium and continues to influence the body economy long after therapy has been stopped.

4. Of 20 reported patients with angina pectoris treated with EDTA, 19 survivors obtained unusual symptomatic relief. The abnormal electrocardiograms of 6 patients reverted to normal patterns under EDTA therapy. In 7 there were fixed changes of old myocardial infarctions.

5. Patients with angina pectoris due to medial sclerosis of the coronary arteries may not be influenced by EDTA.

6. The pathological serum stability reverted toward normal during EDTA therapy in the patients examined.

7. The evidence in support of an intimate relationship between calcium and cholesterol in the atheromatous matrix is discussed.

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(Interlingua on page 718)

PSEUDOMEMBRANOUS COLITIS COMPLICATING PROLONGED ANTIBIOTIC THERAPY

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While the benefits of antibiotic therapy today are obvious, perhaps too little attention has been paid to the complicating effect of prolonged antibiotic therapy, particularly upon the gastrointestinal tract. Reiner, Schlesinger, and Miller[13] reported 7 cases of pseudomembranous colitis following Aureomycin and chloramphenicol therapy. Although one might question the use of this term as descriptive of the lesion, we will follow their terminology.

Janbon, Bertrand, Salvaing, and Labange[4] first observed the appearance of large numbers of coagulase-positive staphylococci in the intestines of patients treated with Terramycin. They reported 2 fatal cases of colitis.

Kleckner, Bargen, and Baggenstoss[6] reviewed the records of the Mayo Clinic for the years 1940 to 1950 and found 14 cases of pseudomembranous colitis, in 7 of which these lesions were considered to be the cause of death. They concluded, however, that there was no increase in the incidence of pseudomembranous colitis since the use of antibiotic agents.

The purpose of this paper is to report 17 cases of pseudomembranous colitis diagnosed post-mortem in this hospital in a 4-year period (an incidence of 1% of all necropsies) and to discuss some of the possible mechanisms that may operate.

In presenting this series of cases it should be indicated that we are fully aware that a somewhat similar lesion may occur in cases that have not received antibiotics. Further attention and interest in the problem, however, may help in the evaluation of this lesion under various conditions.

Material and Methods. Table 1 gives a summary of the 17 cases, indicating the extent and degree of lesions, clinical diagnosis, and antibiotics that were administered. Pseudomembranous colitis occurred in all decades of life, the second decade being the only exception in this series. Although the number of cases is not large enough to draw statistically significant conclusions, there is a definite preponderance in males (14 of 17); however, the male:female ratio in this institution is about 1.8 to 1.0. The latter observation is in contrast with the findings of Reiner, Schlesinger and Miller[13] that the lesions are much more common in females. The incidence can only be evaluated in relation to the number of necropsies performed in this department during the same interval, which was 1,505, that is, about 1% of all necropsies showed pseudomembranous colitis. As might be expected a large number of antibiotics were given. Of the 17 cases, 8 received streptomycin, 7 Terramycin, 6 penicillin, 4 Achromycin, 3 Duracillin, 2 Aureomycin, 1 Chloromycetin, 1 erythromycin, 1 bacitracin, 1 Gantrisin, 1 Rimifon, 1 INAH, and 1 PAS.

In two-thirds of the cases more than one of these drugs were given. Five of these patients suffered from severe infectious diseases, such as tuberculosis, which required extensive antibiotic therapy. Eight cases had malignancies, 4 of the gastrointestinal and 2 of

TABLE 1.—PSEUDOMEMBRANOUS COLITIS, POSTMORTEM OBSERVATIONS IN UNIVERSITY OF WISCONSIN HOSPITALS, 1951–1954

No.	*Case*	*Age*	*Sex*	*Antibiotic Treatment*	*Clinical Diagnosis*	*Location of Lesion*	*Degree*	*Intestinal Bacteriology*
1	C.R.	39	M	Streptomycin, Duracillin	Pulmonary tuberculosis	Entire colon and rectum	4+	
2	M.N.	64	M	Chloromycetin, Terramycin	Tuberculous meningitis	Entire colon and rectum	3+	
3	F.D.	73	M	Terramycin	Carcinoma, rectum	Cecum and sigmoid	3+	
4	I.W.	83	M	Streptomycin	Carcinoma, stomach	Terminal ileum, colon, and rectum	3+	
5	R.D.	2	M	Aureomycin, Penicillin	Purulent meningitis	Entire colon and rectum	4+	
6	F.V.	62	M	Terramycin, Streptomycin, and Penicillin	Carcinoma, esophagus and cecum		2+	
7	F.J.S.	71	M		Cirrhosis-Alcoholism	Cecum	2+	
8	C.M.	56	M	Erythromycin, Penicillin	Purpura, aplastic anemia	Entire colon and rectum	3+	
9	G.R.	52	F	(Roentgen-ray)	Multiple myeloma	Entire colon and rectum	2+	
10	H.S.	22	M	Aureomycin, Terramycin, Bacitracin, Erythromycin	Hodgkin's disease	Sigmoid	2+	*Staph. aureus* cultured
11	W.D.	48	M	Rimifon, Achromycin	Pulmonary tuberculosis	Ascending colon, ileum, and peritonitis	2+	
12	T.A.	57	M	Duracillin	Carcinoma of thyroid and agranulocytosis	Entire colon and rectum	4+	*Staph. aureus* cultured
13	A.N.	60	M	Streptomycin, INAH, and PAS	Pulmonary tuberculosis	Entire colon and rectum and rupture of ileum	4+	*Staph. aureus* cultured
14	W.T.	80	M	Terramycin, Gantrisin, Penicillin, Achromycin, and Streptomycin	Carcinoma of bladder with pressure on rectum	Entire colon and rectum	2+	*Strongyloides* in stools
15	H.S.	54	F	Streptomycin, Terramycin, Achromycin, and Penicillin	Carcinoma of cervix	Entire colon, rectum, and terminal ileum	4+	Gram-positive cocci in section
16	J.M.	2	F	Terramycin (Amino-anfol)	Sympathicoblastoma	Ileum and colon, focal	3+ 1+	
17	E.S.	64	M	Streptomycin, Achromycin, and Duracillin	Carcinoma of rectum	Entire colon and rectum	3+	Gram-positive cocci in smear

the genitourinary tract, 1 of the thyroid gland, and 1 of the adrenal gland. The rest were single cases of Hodgkin's disease, multiple myeloma, aplastic anemia, and cirrhosis.

Grossly the entire colon and rectum were involved in 11 cases, the cecum only in 2 cases, the sigmoid colon only in 1 case, the sigmoid and cecum in 1 case, the ascending colon in 1 case, and the terminal ileum in 5 cases. In one of the cases where the ileum was involved, there was peritonitis, and in another there was rupture of the ileum. In one case there was a paracolic peritoneal abscess. The latter findings are of importance, since rupture has not been emphasized in the cases previously reported in the literature.

The degree of involvement has been graded from 1 to 4 on the basis of an estimation of the number of membranous nodules observed on the mucosal surfaces. Grade 1+ is used to describe the bowel with widely separated nodules, grade 4+ is used when the nodules become confluent, and grades 2+ and 3+ are used to describe the intervening stages.

Bacteriological examination of the fecal content of the colon was only performed in a few cases. *Staphylococcus aureus* was identified in 3 cases and *Strongyloides stercoralis* in one. In one case the Gram-positive cocci were found in a smear of the stools, and in another case they were found in a section.

In 2 cases where further studies were done, the staphylococci were found to be coagulase-positive, sensitive to 10 mg. Chloromycetin, but resistant to 60 mg. Terramycin, and 10 units penicillin.

Pathological Findings. GROSS EXAMINATION. The gross appearance of the colonic mucosa is characterized by numerous elevated nodules measuring about 0.5 cm. in diameter (Fig. 1). The color is yellowish gray, and the consistency is soft. The nodules are firmly adherent to the mucosa and cannot be readily removed. They usually stand out against the background of a congested mucosa. The rectum, the sigmoid, and the cecum are most extensively involved, and the nodules here are often confluent, forming yellowish gray membranes. Evidently they may become detached during life and are found in the stools as casts of the intestinal mucosa, as observed by Williams[17]. The density of these nodules is usually less in the descending, transverse, and ascending colon, but in the most severe cases even these segments become markedly involved. The ileum has only occasionally been found to be involved.

MICROSCOPIC EXAMINATION. The most conspicuous histological picture is observed in the cross section of one of the nodules (Figs. 2 and 3). The mucosa is markedly edematous, and the intestinal glands are dilated. The lumina of the glands are filled by a slightly basophilic mucous material. As the production of mucus increases, the glands form large cysts, the lining epithelium becomes flattened, and cells or sheets of cells are often found desquamated into the lumen. Covering the mucosa is a fibrinous eosinophilic material which contains fragments of necrotic glandular epithelium. In the deeper layers there is usually little or no evidence of inflammation, while the outer layers of the membranes are infiltrated by polymorphonuclear leukocytes. Because of the necrotic appearance of the mucosa, there is no sharp line of demarcation between the membrane and the mucosa. Since the basement membrane is destroyed, it offers no help in orientation. The submucosa is congested and edematous. In the most advanced cases with rupture and peritonitis, a severe inflammatory response is present.

Discussion. The high incidence of pseudomembranous colitis, in our experience, suggests that it is a disease which has increased since the use of antibiotic therapy. In our material of 17 cases, only one patient had no definite history of being treated with antibiotics, while most of the patients were treated with several drugs. There is substantial evidence that antibiotic therapy will change the normal host

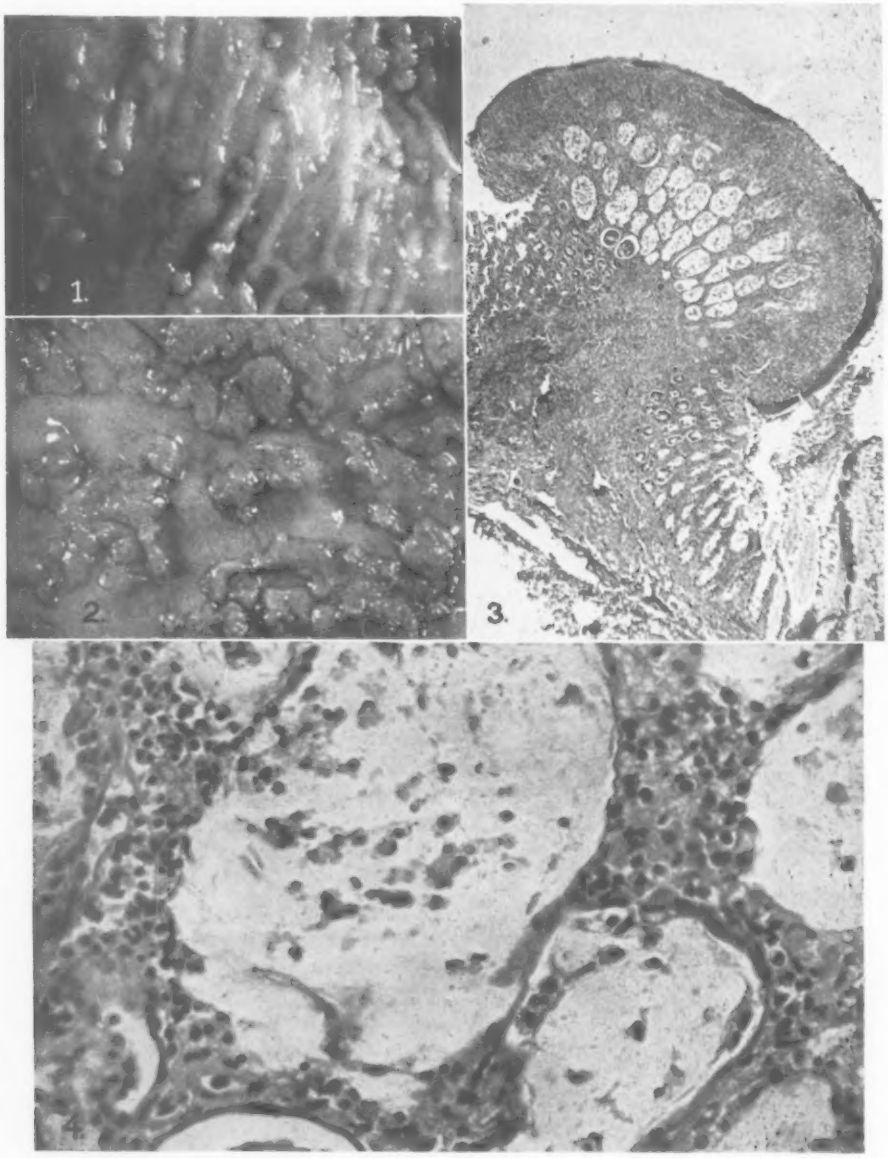

Fig. 1.—To illustrate early discrete nodular lesions of mucosa of colon.

Fig. 2.—A later stage of nodular mucosal lesion to illustrate the confluent pattern (Case 5).

Fig. 3.—Section to demonstrate dilated glands, edematous stroma, and superficial deposition of fibrin with inflammatory cell infiltration. (× 35.)

Fig. 4.—Dilated intestinal glands filled with mucus and desquamated epithelial cells and surrounded by inflammatory cells. (× 300.)

flora when administered over a long period of time (McCoy[8]). The development of a secondary flora is often responsible for failures of antibiotic therapy. Most spectacular is the occurrence of a nearly pure culture of *Staphylococcus aureus (M. pyogenes)* in the feces. Dearing and Heilman[2] found this organism to be predominant in the intestinal flora of 44 patients who had been treated with Terramycin.

Finland and Weinstein[3] found that *Staphylococcus aureus* started to multiply rapidly in the intestines of patients treated with antibiotics such as Terramycin, Aureomycin, and chloramphenicol and that this change occurred about the fourth day of treatment.

Although the staphylococci are not normally prevalent among the intestinal microörganisms, they are present in a large percentage of the population. Oeding and Austarheim[9] found staphylococci at necropsy in the intestinal content of 17% of nontreated patients and 26% of patients treated with various antibiotics. While many investigators emphasize the occurrence of staphylococci, little effort has been made to determine the quantitative proportion of staphylococci in relation to the other intestinal microörganisms in patients with pseudomembranous colitis. Lately Rieckert[14] who reports 11 cases points out that he was unable to isolate any staphylococci in 5 cases which were examined bacteriologically. On the other hand there was a preponderance of Proteus which were antibiotic-resistant.

Because of these discrepancies it seems logical to consider a change in host resistance to normally occurring intestinal microörganisms. Undoubtedly a multitude of factors may influence the normal host resistance, and in searching for such factors an analysis of the reported cases may be useful. At least 6 of our 17 cases had evidence of intestinal obstruction prior to the development of colitis. This is in accord with Pettet *et al.*[11] who reported a 44% incidence of obstruction on the basis of carcinomas. Since most patients with gastrointestinal carcinomas are extensively treated with antibiotics, fatal colitis must occur only in a small percentage. Five of our 17 patients had tuberculosis, and were treated with antibiotics for a considerable period. It has also been shown that the absence of certain vitamins will produce gastrointestinal symptoms and lesions. Schaefer, McKibbin and Elvehjem[15] have described sudden prostration and coma with gastrointestinal symptoms in dogs which were deficient in pantothenic acid. Wintrobe *et al.*[18] observed an extensive colitis in swine on a pantothenic acid deficient diet. Pantothenic acid deficiency is rare in humans, presumably because many strains of *E. coli* (Jannes[5]) synthesize this vitamin. However, after prolonged antibiotic therapy with depression of *E. coli*, this useful synthesis may be reduced or even abolished.

It has been shown by Sevag and Green[16] that pantothenic acid is required for the building of tryptophan by certain strains of *Staphylococcus aureus*. Many other intestinal microörganisms, among them *Proteus morganii* (Porter[12]), likewise require pantothenic acid for their growth. If pantothenic acid-requiring organisms such as *Staphylococcus aureus* and *Proteus morganii* predominate in the fecal flora, a deficiency may conceivably be produced in the host. It also has been shown that pantothenate deficient hosts may lose their innate resistance to infection with a type of microörganism which is part of their normal flora (Zucher and Zucher[19]). Finally, it should be mentioned that Penner and Drucherman[10] were impressed by the fact that shock was

commonly present in all their cases of enterocolitis. A severe drop in blood pressure (shock) may also reduce host resistance against the intestinal flora and cause a lesion such as postoperative enterocolitis. Anatomically, however, the latter is characterized by continuous and loosely attached membranes predominantly in the small intestine, and, therefore, differs in many respects from the nodular and firmly attached lesion in the colon described here.

Summary. A review of various concepts of pseudomembranous colitis is given. Seventeen cases diagnosed at time of necropsy are reported and classified according to the pathologic anatomical picture. Pseudomembranous colitis occurred in about 1% of about 1,500 necropsies.

The patients were treated with large doses of antibiotics over a long period of time. Eight received streptomycin, 7 Terramycin, 6 penicillin, 4 Achromycin, 3 Duracillin, 2 Aureomycin, 1 Chloromycetin, 1 erythromycin, 1 bacitracin, 1 Gantrisin, 1 Rimifon, 1 INAH, and 1 PAS. We are in agreement with earlier observers that changes of intestinal bacterial flora play an important role in the pathogenesis of pseudomembranous colitis. *Staphylococcus aureus* was isolated in some of our cases, but was absent in others. On the other hand, *Staphylococcus aureus* has been isolated from the intestines of many hospital patients who never develop this lesion. It is also recognized that other organisms, such as *Proteus vulgaris*, have been found to predominate in the intestines of patients with pseudomembranous colitis. A possible explanation to these seeming discrepancies may be that antibiotic therapy sometimes reduces *E. coli*, and other vitamin synthesizing microörganisms, and favors the growth of vitamin requiring microörganisms, among which we find *Staphylococcus aureus* and *Proteus vulgaris*. Pseudomembranous colitis may thus be a manifestation of vitamin deficiency.

The following facts would tend to support such a concept:

1) Dogs, swine and other animals are known to develop an intestinal lesion when fed a pantothenic acid deficient diet.

2) Patients with pseudomembranous colitis often have cancer of the gastrointestinal tract or other wasting diseases which may be associated with vitamin deficiences.

3) Long range antibiotic therapy will decrease the pantothenic acid synthesizing *E. coli* and increase the growth of pantothenic acid requiring organisms such as *Staphylococcus aureus* and *Proteus vulgaris*.

Such a postulation will of course depend upon further experimental studies to support it.

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SUMMARIO IN INTERLINGUA

Colitis Pseudomembranose, Complicante le Prolongate Therapia a Antibiotico

Es presentate un revista de varie conceptiones de colitis pseudomembranose. Es reportate 17 casos diagnosticate al necropsia. Illos es classificate secundo lor aspectos pathologico-anatomic. Colitis pseudomembranose esseva trovate in circa 1% de un serie de 1.500 necropsias.

Le patientes esseva tractate con grande doses de antibioticos durante longe periodos. Octo recipeva streptomycina, 7 Terramycina, 6 penicillina, 4 Achromycina, 3 Duracillina, 2 Aureomycina, 1 Chloromycetina, 1 erythromycina, 1 bacitracina, 1 Gantrisina, 1 Rimifon, 1 NAH, e 1 PAS. Nos es de accordo con previe observatores que alterationes del flora bacterial intestinal ha un rolo importante in le pathogenese de colitis pseudomembranose. *Staphylococcus aureus* esseva isolate in certes de nostre casos sed esseva absente in alteres. Del altere latere, *St. aureus* ha essite isolate ab le intestinos de multe patientes hospitalisate qui nunquam disveloppava le lesion his discutite. Nos es etiam conscie del facto que altere organismos, per exemplo *Proteus vulgaris,* ha essite incontrate como organismo predominante in le intestinos de patientes con colitis pseudomembranose. Un explication possibile de iste apparente contradictiones es forsan que le therapia antibiotic reduce a vices *E. coli* e altere microorganismos que produce vitamina a promove le crescentia de microorganismos que require vitamina. In iste ultime classe nos trova *St. aureus* e *P. vulgaris.* Colitis pseudomembranose esserea alora un manifestation de carentia de vitaminas.

Le sequente factos pare supportar un tal conception:

1. Il es cognoscite que canes, porcos, e altere animales disveloppa un lesion intestinal quando lor dieta es deficiente in acido pantothenic.

2. Patientes con colitis pseudomembranose ha frequentemente cancere del vias gastro-intestinal o altere morbos consumptive que es possibilemente associate con carentia de vitaminas.

3. Therapia antibiotic a longe durantia reduce *E. coli* que synthetisa acido pantothenic e promove le crescentia de organismos que require acido pantothenic, per exemplo *S. aureus* e *P. vulgaris.*

Il va sin dicer que le postulato hic presentate require le supporto de additional studios experimental.

ACUTE MENINGOCOCCEMIA WITH VASCULAR COLLAPSE: AN ANALYSIS OF 10 RECENTLY TREATED CASES

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Acute meningococcemia with vascular collapse was almost uniformly fatal prior to the advent of the sulfonamides. This classically fatal syndrome, marked by petechial eruptions, shock, and adrenal hemorrhages at necropsy, was first extensively reported by Waterhouse[24] and Friderichsen[9]. With the use of the sulfonamides and penicillin the results in all types of meningococcal infection were greatly improved, although the mortality rate in the Waterhouse-Friderichsen syndrome continued to be extremely high (Kinsman, D'Alonzo and Russi[15], Banks[2]). In 1948, Brand[4] reviewed 25 cases with recovery and added one of his own. Williams[26] in 1942 reported hemorrhage in the adrenals of only 9 of 17 patients with the Waterhouse-Friderichsen syndrome, although previous reports (Aegerter[1]) had emphasized the almost universal finding of bilateral adrenal hemorrhages in these cases. Rich[22] was able to explain this apparent discrepancy by noting microscopic evidence of adrenal cortical cell degeneration in several cases of the Waterhouse-Friderichsen syndrome not showing gross hemorrhage. His work strongly suggested that the circulatory collapse occurring in severe infection is either due to or accompanied by acute functional adrenal insufficiency. Adrenal cortical extract and sodium chloride have been used often to combat the peripheral vascular collapse noted in this syndrome, and in other kinds of septicemia, with varying results (Perla and Marmorston[20], Grubschmidt, Graham and Jessup[11]; Lepper *et al.*[16]). Adrenal replacement therapy with cortisone in this syndrome was first reported by Nelson and Goldstein[18]. Since their report in 1951, a score of case reports on the successful treatment of this syndrome with cortisone alone and in combination with norepinephrine have appeared[3,5,10,12,13,14,17,19,23,25]. With the use of antibiotics, potent adrenal cortical hormones, and norepinephrine the mortality rate in the Waterhouse-Friderichsen syndrome has been lowered but remains formidable.

It is the purpose of this paper to present our experience with a comparatively large number of these cases recently treated. All of them had proven meningococcal septicemia complicated by profound vascular collapse. Certain therapeutic considerations will be emphasized which may help reduce the

over-all mortality rate in this devastating condition. The 10 cases herein reported were treated at an Army Hospital during the years 1953 to 1955; and they comprised 11% of all admissions for meningococcal disease at that hospital. The great majority of these patients were recruits who had been in service less than two months.

Case Reports. CASE 1. This 20-year-old inductee with 3 weeks' service was admitted to the hospital on February 22, 1955, in a delirious state with a temperature of 106°. He had noted chilly sensations and fever together with a mild headache for 8 hours prior to admission. Twelve days before, he had been treated in the hospital for an acute pharyngitis with terramycin, 1 gm. daily for 5 days, as well as symptomatic therapy. He had been afebrile and asymptomatic for 3 days prior to his discharge from the hospital at that time.

Physical examination revealed temperature 106°, pulse 130 per minute, respirations 26, blood pressure 65/0. The skin was covered with petechiae and ecchymoses, many of which had raised necrotic centers. There was moderate injection of the pharynx. The lungs were clear, the heart not enlarged, its rate 130 per minute. There were no murmurs. A–2 was greater than P–2. Abdominal examination was negative. There was moderate stiffness of the neck. The patient was irrational and thrashing about wildly. The reflexes were normal. The remainder of the examination was negative. Laboratory data included: leukocytes 27,000 with 90% neutrophils, 10% lymphocytes, hemoglobin 14 gm.; sedimentation rate 30 mm. per hour. No urine was obtained. The spinal fluid was cloudy and contained 600 leukocytes per c.mm., 90% of which were neutrophils; Gram-negative intracellular diplococci were demonstrated on smear of the spinal fluid. Total circulating eosinophil count was 67 per c.mm.

HOSPITAL COURSE: A diagnosis of meningococcic meningitis with fulminating meningococcemia and shock was made and treatment instantly begun with 2 gm. of Gantrisin and 1,000,000 units of aqueous crystalline penicillin given I.V., 200 mg. of cortisone given I.M., and 50 ml. of aqueous adrenal extract given I.V. An intravenous infusion of norepinephrine (levophed bitartrate) at a rate of 2 to 3 μg. per minute was administered. Increasingly large quantities of norepinephrine were necessary during the succeeding hours to maintain the blood pressure above shock levels. Four hours after admission he was receiving 64 μg. of norepinephrine per minute. There was no urine output throughout the entire hospitalization. Respirations became labored at a rate of 30 per minute and many rhonchi were heard throughout the chest. Six hours following therapy the temperature fell to 101° but the blood pressure was no longer obtainable. The norepinephrine infusion was increased to 130 μg. per minute. However, the pressure could not be raised above 50 mm. systolic. The patient expired 9 hours after hospitalization. Total therapy administered consisted of 8 gm. of Gantrisin I.V., 1,000,000 units of aqueous crystalline penicillin I.V., and 3,000,000 units of aqueous crystalline penicillin I.M., 250 mg. of cortisone I.M., 430 ml. of aqueous adrenal extract I.V. in divided doses of approximately 30 ml. every half hour. A total of 60 mg. of norepinephrine was given during the 9 hours of hospitalization. Four liters of intravenous fluid were administered: only 5% dextrose in water, no saline.

NECROPSY FINDINGS: Acute meningococcic septicemia. Massive hemorrhage into the adrenal glands bilaterally. Diffuse petechial and ecchymotic hemorrhages of the skin, mucous membranes and serosal surfaces throughout the body. Terminal hypostatic congestion of the lungs. Congestion and edema of the brain. Microscopic examination of the heart revealed foci of petechial hemorrhage throughout the endocardium, myocardium, and epicardium. Both lungs revealed ecchymotic hemorrhagic areas throughout the parenchyma, especially in the dependent portions. The adrenal glands microscopically showed nearly complete destruction of both glands by the hemorrhagic process. The brain showed moderate congestion of the meningeal vessels; microscopic section revealed scattered foci of hemorrhage within the outer layers of the cortex, but no frank purulent exudate. The kidneys grossly were normal except for the presence of small ecchymotic areas under the capsule of both kidneys. Microscopically some of the tubules were dilated and filled with a homogeneous material that resembled colloid; in these tubules the epithelium was thin and showed varying degrees of degeneration. There was marked congestion of the renal vessels.

CASE 2. This 18-year-old white male with one month's service in the Army was admitted to the hospital on March 5, 1955, in a state of profound shock. Twelve hours before admission he had felt well and was carrying

on normal duties. About 4 hours before admission he felt drowsy, noted a headache, and vomited several times. He walked to the dispensary and then collapsed. Past history was essentially negative.

Physical examination revealed a moribund semicomatose individual in profound shock. The blood pressure was 0, pulse 140 per minute and barely perceptible, respirations 18, rectal temperature 102°. The eyes were injected and wandering aimlessly. The pupils reacted to light. There was moderate cyanosis. The pharynx was injected. There was no venous distention. The lungs were clear, the heart not enlarged, its rate 140 per minute, sounds weak and of very poor quality. A–2 was equal to P–2. No murmurs or rubs were present. Abdominal and rectal examinations were negative, the genitalia normal. No lymph glands were palpable. There were many small and medium-sized petechiae over the entire body with medium-sized ecchymoses on the ankles, shins and abdominal wall. The patient was unresponsive. The cranial nerves were intact. There was slight resistance to flexion of the neck. The deep tendon reflexes were active and equal bilaterally. Babinski and Hoffman signs were negative. The remainder of the examination was within normal limits. Laboratory data included: 25,000 leukocytes per c.mm. with 87% neutrophils, 16 of which were bands, and 13% lymphocytes. Hemoglobin was 13 gm., hematocrit 41%, sedimentation rate 29 mm. per hour. Urine was normal except for 4+ albumin. Initial circulating eosinophil count was 60 cells per c.mm.

HOSPITAL COURSE: A diagnosis of Waterhouse-Friderichsen syndrome was made and therapy immediately instituted. In order to restore the blood pressure to normal levels an I.V. infusion of norepinephrine at a rate of 160 μg. per minute was necessary.

Four grams of Gantrisin and 1,000,000 units of aqueous crystalline penicillin were given I.V., and thereafter 2,000,000 units of aqueous crystalline penicillin every 2 hours were given I.M., and 100 mg. of hydrocortisone and 100 ml. of aqueous adrenal extract I.V. A total of 200 mg. of cortisone was given I.M. in 4 separate injection sites, also 500 mg. of ascorbic acid I.V. Four hours after the institution of therapy the patient had improved. Blood pressure was maintained at 100/60. Urine output was good. Four hours after institution of therapy there were no circulating eosinophils. The patient was digitalized with 1.6 mg. of Lanatoside-C intravenously. An oxygen tent was used because of mild cyanosis and a respiratory rate of 30 per minute, although the lungs were clear. An electrocardiogram showed a sinus tachycardia of 120 with flat T waves in Leads 1, 2, 3, aVR, aVL and diphasic T waves in Leads V1 to V6. During the first 24 hours the patient received a total of 6 liters of fluid and medication intravenously; 500 ml. of which was normal saline. The urine output was 4.2 liters and there were 550 ml. of vomitus. A total of 16 gm. of Gantrisin I.V., 100 mg. of hydrocortisone I.V., 350 mg. of cortisone I.M., 800 ml. of aqueous adrenal extract, and 168 mg. of norepinephrine were given I.V. during the first 24 hours, and 12,000,000 units of aqueous crystalline penicillin I.M. On the second day of hospitalization the leukocytes numbered 52,600 per c.mm., with 94% neutrophils and 6% lymphocytes; no eosinophils. The initial blood culture was positive for Meningococcus Type II. At the end of the second day the patient was lucid for the first time. During the second 24 hours of hospitalization, he received 4,800 ml. of intravenous fluids, 500 ml. of which was normal saline, 200 mg. of cortisone I.M., 220 ml. of aqueous adrenal extract I.V., 16 gm. of Gantrisin I.V., 12,000,000 units of aqueous crystalline penicillin I.M., 48 mg. of norepinephrine I.V., and 3 gm. of potassium chloride I.V. The urine output was 4,800 ml. On the third hospital day, a striking improvement was noted. The norepinephrine infusion was discontinued, the patient maintaining a blood pressure of 160/70. Pulse was 110 per minute. Lungs were clear. The electrocardiogram continued to show flat T waves in all leads. Temperature was 100.5°. Sodium was 132 mEq./L., potassium 4.3 mEq/L., CO_2, 64 volumes %, chloride 97.5 mEq./L., BUN 16 mg. per 100 ml. The urine output was good and the patient began to take fluids by mouth. Aqueous crystalline penicillin and Gantrisin were gradually reduced in amount and stopped completely on the tenth day. Cortisone was gradually reduced and discontinued on the fourteenth day. He received 40 mg. of ACTH I.M. on the fifteenth day and 20 mg. on the sixteenth day. The only residual abnormality noted during convalescence was a right partial median nerve palsy with moderate hypesthesia and motor weakness of the first two fingers of the right hand. There were no signs of chronic adrenal insufficiency. The patient felt well 3 weeks after the onset of the illness and all laboratory findings, including the electrocardiogram, became normal. A 17-ketosteroid excretion of 14 mg. per 24-hour urine collection and a normal fall in circulating eosinophils from 130 to 30 per c.mm. follow-

ing the I.V. administration of 20 mg. of ACTH over an 8-hour period were demonstrated during the third week of convalescence.

CASE 3. This 21-year-old white male with one week's service in the Army was admitted to the hospital on March 2, 1955, because of a sore throat, weakness, and diarrhea of 2 days' duration. Past history was essentially negative.

Physical examination revealed an acutely ill, moribund male who was confused and disoriented. Temperature was 102.6°, pulse 130, respirations 20, and blood pressure 50/0. There were many small petechiae and medium-sized ecchymoses over the entire body; many of these had necrotic centers. The pharynx was acutely injected without exudate. The lungs were clear, the heart not enlarged, its rate 130 per minute. No murmurs or rubs were present. A–2 was greater than P–2. Abdominal examination was not remarkable. Neurological examination revealed intact cranial nerves, equal and active reflexes, no nuchal rigidity. Sensorium was intermittently clouded and confused. Laboratory data included a leukocyte count of 16,200, with 87% neutrophils, 12% lymphocytes, 1% eosinophils. Hemoglobin was 13.8 gm., hematocrit 44%. Initial urine revealed specific gravity 1.013, faint trace of albumin, no sugar; microscopic: 4 red cells, occasional white cells, and 1 small finely granular cast/hpf. Total circulating eosinophil count was 80 cells per c.mm.

HOSPITAL COURSE: A diagnosis of meningococcic septicemia with vascular collapse was made and therapy instantly begun with 1,000,000 units of aqueous crystalline penicillin, 2 gm. of Gantrisin, 60 ml. of aqueous adrenal extract, and 100 mg. of hydrocortisone given I.V., and 120 μg. per minute of norepinephrine were administered I.V. in order to bring the blood pressure up to 100/60. Eight hours after admission, it was necessary to give 160 μg. of norepinephrine I.V. per minute. The patient was digitalized with 1.6 mg. of Lanatoside-C I.V. over a 24-hour period as a prophylactic measure. During the first 24 hours 6,000,000 units of aqueous crystalline penicillin I.M. and 1,000,000 units I.V., 18 gm. of Gantrisin with a Gantrisin blood level of 14 mg. of free drug, 3 liters of 5% glucose in water, 1 liter of physiological saline, 1 liter of aqueous adrenal extract I.V., 100 mg. of hydrocortisone I.V. and 200 mg. of cortisone I.M. were given. Output during the first 24 hours consisted of 350 ml. of urine, and 700 ml. of vomitus. On the second day the blood pressure was stabilized at 110/70 with the norepinephrine infusion continuing. The lungs were clear; the heart sounds of good quality at a rate of 100. The electrocardiogram showed a sinus tachycardia with flat T waves in all leads. Blood analyses included: Blood urea nitrogen 42 mg. per 100 ml., CO_2, 47 volumes %, chloride 92 mEq./L. Blood culture yielded a Type I Meningococcus. On the third day, urine output was 60 ml. and the problem of fluid and electrolyte balance had become critical. The hematocrit was 32%, having been 44% on admission. Intravenous fluids were restricted to 1,200 ml. of 5% glucose in water. The intravenous administration of norepinephrine was gradually decreased and on the third day his blood pressure was maintained at normal levels without the use of this drug. Cortisone was continued in a dosage of 50 mg. I.M. every 6 hours, and 1,000,000 units of aqueous penicillin were given I.M. every 6 hours. With renal shutdown, the Gantrisin blood level continued to be 14 mg. per 100 ml., so that only small quantities of that drug were given during the next 2 days. His general clinical condition seemed improved except for the renal shutdown. The serum sodium was 123 mEq./L., potassium 7.3 mEq./L., blood urea nitrogen 57 mg. per 100 ml. The electrocardiogram showed a nodal rhythm at a rate of 100 and a progressive widening of the QRS complex to 0.12 second with peaking of the T waves. Despite the administration of 10% glucose in water containing calcium gluconate and insulin, the serum potassium continued to rise. It was felt that the use of an "artificial kidney" for dialysis of the serum potassium was crucial. He was transported expeditiously and with no detectable deterioration in his condition to a Medical Center where dialysis was performed on the fourth hospital day. A marked improvement in the electrocardiogram occurred following dialysis; the serum sodium was 130 mEq./L., potassium 4.9 mEq./L. (having been 8.8 mEq./L. prior to dialysis), chloride 86 mEq./L., CO_2 17 volumes %, and blood urea nitrogen 67 mg. The leukocytes numbered 23,600 per c.mm., with 96% neutrophils and 4% lymphocytes. The hematocrit was 28%, hemoglobin 9.7 gm.

On the fifth day the blood pressure remained stable at 120/60. The temperature was 99.8°. However, the patient again became semi-comatose. Neurological examination revealed blurring of both optic disks, with the left pupil larger than the right. The deep tendon reflexes were hypoactive. A tap revealed a pressure of 420 mm. of water with 86 white cells per c.mm., 80% of which

were neutrophils; the total protein was 58 mg. per 100 ml. Chest film revealed bilateral pulmonary infiltration, more marked on the left, thought to be compatible with bronchopneumonia. On the fifth day he received 1,000 ml. of 5% glucose in water. Urinary output was 125 ml. and vomitus 400 ml. On the sixth day, 525 ml. of intravenous fluids were given. The urine output was 90 ml. A transfusion of 300 ml. of packed washed red cells was given, following which the venous pressure in the right antecubital vein was 110 mm. of water. Chest film revealed an increase in the scattered mottling throughout both lung fields. Blood urea nitrogen was 160 mg., sodium 135 mEq./L., potassium 6.4 mEq./L., CO_2, 22 volumes %, chloride 92 mEq./L. The leukocytes were 55,000 per c.mm., with 83% neutrophils, 27 of which were bands; 12% lymphocytes and 5% eosinophils. The urine had a specific gravity of 1.020, 3+ albumin, 100 red cells/hpf, and no sulfa crystals. Rapid shallow respirations, increasing cyanosis, and deep coma supervened. On the seventh day the blood pressure was 138/76, the pulse 110 per minute, respirations were 36 per minute, and temperature was 99.4°. The patient suddenly became very restless and expired.

PATHOLOGIC DIAGNOSES: Massive adrenal hemorrhages were found. The hemorrhages involved the entire gland bilaterally and only a thin rim of adrenal cortical tissue could be identified. The brain was extremely edematous and soft, weighing 1,525 gm. There was a mild pressure conus present bilaterally. The cerebral spinal fluid was red-tinged, but not purulent. A culture of heart, blood, and cerebral spinal fluid showed no growth. The lungs showed a diffuse lobular pneumonia with marked pulmonary edema, and an effusion of 300 ml. in the left pleural cavity. The heart showed a slightly dilated right ventricle with many pericardial petechial hemorrhages. Otherwise, the heart was normal. The kidneys were large and edematous; no petechial hemorrhages were noted. A moderate amount of tubular cell necrosis was present.

CASE 4. This 22-year-old Negro male had had a sore throat, headache, and weakness for 2 days. He had been in service for 2 months and was admitted to the hospital on June 11, 1954.

Physical examination revealed an acutely ill male with blood pressure of 60/30, pulse 130 per minute, temperature 103°. The pharynx was injected and the neck rigid. The remainder of the examination was negative. The spinal fluid was turbid with many Gram-negative intra- and extra-cellular diplococci on smear. A diagnosis of meningococcic meningitis and Waterhouse-Friderichsen syndrome was made and therapy immediately instituted. The patient was in profound shock for 4 hours, after which time the blood pressure slowly rose to normal, but 18 hours after admission he developed acute congestive heart failure and anuria. Despite the use of intravenous Lanatoside-C, rotating tourniquets, and oxygen, there was no improvement and he expired suddenly 22 hours after admission. Total medication administered consisted of 6 gm. of Gantrisin I.V., 8 gm. of Gantrisin I.M., 300 mg. of cortisone I.M., 50 ml. of aqueous adrenal extract I.V., and 1.6 mg. of Lanatoside-C I.V. He received 3 liters of intravenous fluids: 1,500 ml. normal saline, 1,000 ml. 5% glucose in water, and 500 ml. of 0+ compatible whole blood. Total urine output was 200 ml.

NECROPSY FINDINGS: Bilateral massive hemorrhage into both adrenal glands was found with extensive destruction of adrenal tissue. The brain showed an inflammatory exudate around the base with small foci of hemorrhage in the brain tissue. The heart had foci of hemorrhage throughout the myocardium. There were no signs of acute cardiac dilatation. The lungs were edematous, oozing much frothy blood fluid on section. The gastrointestinal tract had many scattered petechiae and purpuric areas, chiefly in the ileum. The kidneys had petechiae in the pelvic mucosa bilaterally and on microscopic section a generalized hyperemia with some hemorrhage into the kidney tubules was noted.

CASE 5. A 19-year-old recruit with 10 weeks' service was admitted to the hospital on April 17, 1954, because of high fever and convulsions. He had noted headache and malaise for 8 hours before admission. Past history was negative.

Physical examination revealed a well developed, well-nourished male, semicomatose and covered with vomitus. Blood pressure was 120/50, pulse 130, temperature 102°; respirations were 20 per minute. Head and neck were negative except for bilateral subconjunctival hemorrhages. The lungs were clear, the heart not enlarged, its rate 130 per minute. The skin was covered with an extensive confluent purpuric eruption. Neurological examination was negative. The initial white cell count was 10,600, with 87% neutrophils. The spinal fluid was normal, with no organisms seen on smear.

Gantrisin therapy was immediately started; 4 gm. were given I.V. over a period of 2

hours in 1 liter of 5% glucose in saline. Two hours later the blood pressure was 120/60; but 2½ hours after admission the patient became very restless and the blood pressure fell to zero. He was livid, markedly dyspneic and in profound shock. Norepinephrine infusion I.V. was immediately started, 100 mg. of hydrocortisone and 50 ml. of aqueous adrenal extract were given I.V. He was placed in an oxygen tent. There was no response in blood pressure. Pulmonary edema developed rapidly and the patient was given 1.2 mg. of Lanatoside-C I.V., but 15 minutes after the onset of shock and 3½ hours after admission he suddenly expired.

NECROPSY FINDINGS: Bilateral massive hemorrhage and necrosis of the adrenal glands, passive congestion of the lungs, petechial hemorrhages through the myocardium, and slight inflammatory changes in the meninges of the brain. Cause of death: Meningococcic septicemia (Waterhouse-Friderichsen syndrome).

CASE 6. This 20-year-old white male with 5 weeks' Army service was admitted to the hospital on April 20, 1955, for fever and sore throat. The patient had had a mild upper respiratory infection for 3 days before admission. Past history was noncontributory.

Physical examination on admission showed only an injected pharynx and a temperature of 100.6°. Three hours later he was drowsy and physical examination showed many petechiae scattered over the entire body. Temperature was 106.5°, pulse 130, and blood pressure 95/45. The lungs were clear, the heart not enlarged. Neurological examination was negative except for a clouded sensorium. Laboratory data included 9,700 leukocytes per c.mm., with 91% neutrophils, 6% lymphocytes, 3% monocytes, and no eosinophils. Hemoglobin was 15 gm./100 ml. The urine was yellow, cloudy, acid, and had specific gravity 1.016. A faint trace of albumin was present. There were 8 red cells and 2 white cells/hpf. Electrocardiogram was normal except for a sinus tachycardia of 120 per minute.

A diagnosis of acute meningococcic septicemia having been made, 4 gm. of Gantrisin and 1,000,000 units of aqueous crystalline penicillin were given I.V. With alcohol sponging, the temperature was brought down to 101°. The blood pressure remained stable at 90/40 for 10 hours after treatment had been instituted, but then fell to 60/20. At this point I.V. norepinephrine was started and the pressure rose to 100/60. He was given 100 mg. of hydrocortisone and 30 ml. of aqueous adrenal extract I.V., and 50 mg. of cortisone I.M. Twenty-four hours after admission he developed a hacking cough with respirations of 30 per minute; coarse rales were heard at the lung bases. He was given oxygen therapy, and digitalized with Lanatoside-C I.V. During the next 12 hours there was moderate improvement in the pulmonary edema. Total I.V. fluids administered during the first 24 hours of admission were 3,700 ml., of which 1 liter was physiological saline. The urinary output was 1,700 ml.

Forty-eight hours after admission, the blood pressure suddenly fell to 0. Norepinephrine was increased to 150 μg. per minute I.V.; 50 mg. of hydrocortisone and 30 ml. of aqueous adrenal extract were given I.V. Despite all this the patient remained in shock with progressing congestive heart failure and he died about 48 hours after the start of therapy. Total medication included 22 gm. of Gantrisin I.V., 1,000,000 units of aqueous crystalline penicillin I.V., 10,000,000 units of aqueous crystalline penicillin I.M., 150 mg. of hydrocortisone I.V., 100 ml. of aqueous adrenal extract I.V., 200 mg. of cortisone I.M., 2.4 mg. of Lanatoside-C I.V., and 7 mg. of norepinehrine I.V. The clinical diagnoses were: Septicemia, meningococcic, acute; with Waterhouse-Friderichsen syndrome; myocarditis, acute, secondary to meningococcemia, with acute congestive heart failure.

NECROPSY FINDINGS: An acute interstitial myocarditis with many focal hemorrhages was noted. The lungs were markedly edematous, with scattered areas of early bronchopneumonia, most of the alveoli and terminal bronchioles were filled with a dense hyaline membrane. The kidneys and brain showed minimal changes. The adrenal glands appeared normal grossly. On microscopic section a generalized hyperemia with occasional focal hemorrhages was noted; both cortical and medullary cells showed many areas of marked vacuolization of the cytoplasm, but nuclear changes were not conspicuous. A heavy scattering of neutrophils, especially in the zona glomerulosa of the cortex, was noted. These adrenal findings were interpreted as consistent with an early premortem necrobiotic process.

CASE 7. This 18-year-old inductee with 3 weeks' Army service developed an upper respiratory infection 4 days before admission on July 1, 1954.

Physical examination revealed temperature 103°, blood pressure 120/60, injected throat, and slight cervical lymphadenopathy. The rest of the examination was negative. Ten hours later he developed a fever of 105°,

frontal headache, and a generalized petechial and purpuric rash. Physical examination at that time revealed an acutely ill male, with blood pressure 110/60, pulse 85, and respirations 20. There was an acute pharyngitis and bilateral subconjunctival hemorrhages. The chest was clear, the heart normal. There were many small petechiae and large confluent ecchymotic lesions over the trunk and extremities. Neurological examination was negative, as was the rest of the examination. Laboratory data included 12,300 white cells per c.mm., with 96% neutrophils, 4% lymphocytes, no eosinophils. Urinalysis and spinal fluid were normal. The blood culture was positive for Meningococcus Type I.

A diagnosis of acute meningococcemia having been made, therapy with Gantrisin was begun. Eight hours after the start of therapy, the blood pressure suddenly fell to 60/40 and the pulse rose to 120 per minute. The temperature was 99.2°. The patient had no complaints. Intravenous norepinephrine therapy was instituted and the blood pressure rose to 90/50. The following medications were given: 100 mg. of hydrocortisone I.V., 20 ml. of aqueous adrenal extract I.V. every hour for 8 hours, 300 mg. of cortisone I.M., 1,000,000 units of aqueous crystalline penicillin I.V., followed by 1 000,000 units of aqueous crystalline penicillin I.V., followed by 1,000,000 units of aqueous crystalline penicillin I.M. every second hour. Fluids were limited to 3 liters of 5% glucose in water during the first 36 hours. The electrocardiogram revealed a sinus tachycardia of 130, a prolonged P–R interval, a progressively increasing intraventricular conduction defect and marked T wave changes. Thirty-six hours after the start of therapy, he developed congestive heart failure. Urinary output was very low and the blood urea nitrogen rose to 70 mg. He was digitalized and placed in an oxygen tent. During the next 2 days his general condition slowly improved, and by the fifth hospital day he was no longer in heart failure. His course was further complicated by many necrotic skin lesions which healed slowly. Convalescence was protracted, and signs of a persistent myocarditis as evidenced by tachycardia at rest, and persistent "T" wave changes in the electrocardiogram were noted. Other abnormalities included a 2+ albuminuria, an elevated sedimentation rate, and a hypochromic normocytic anemia. Liver function tests were normal. He was gradually rehabilitated over a course of 6 months, and then discharged from the Service. There were no clinical or laboratory signs of chronic adrenal insufficiency; the eosinophil response to intravenous ACTH was normal, as was the 24-hour urinary excretion of 17 ketosteroids.

Case 8. This 18-year-old white male with 4 weeks' Army service developed a sore throat and cough 4 days before admission, for which he was given an injection of aqueous crystalline penicillin and aspirin tablets. Two days later he fainted while marching and was brought to the hospital on April 9, 1954, where physical examination revealed a toxic young male, very drowsy and weak. His temperature was 101°, blood pressure 110/60, and pulse 90 per minute. Positive physical findings included: moderate stiffness of the neck, many petechiae and large ecchymoses over the entire body, and a markedly injected pharynx. Examination of the heart was negative except for a Grade II systolic murmur heard loudest in the third left parasternal interspace. Laboratory data included a spinal fluid with 15 neutrophils per c.mm. but otherwise normal; 10,200 leukocytes per c.mm. of blood, with 83% neutrophils and 17% lympocytes. The hemoglobin was 12 gm. %. The urine was negative except for 2+ albumin and 1 to 3 granular casts/hpf. Smear of the serum from a punctured ecchymotic lesion revealed many Gram-negative diplococci, and a blood culture was positive for Meningococcus Type I. The electrocardiogram on admission showed a sinus tachycardia with inverted T waves in Leads 2, 3, aVF, V4, V5, and V6.

Treatment with I.V. Gantrisin was begun at once. Twelve hours after admission the white blood count had risen to 32,000, with 86% neutrophils, and the blood pressure fell to 60/30. Therapy for acute adrenal cortical insufficiency was begun. The patient was given 100 mg. of cortisone I.M. and 50 ml. of aqueous adrenal extract I.V., 500 ml. of normal saline I.V. and 10 mg. of "DOCA" I.M. Within 45 minutes the blood pressure rose to a level of 90/50. Thirty-six hours after admission, the blood pressure was 80/40. He received 200 mg. of cortisone I.M. and 5 ml. of aqueous adrenal extract every half hour I.V. On the third day, with a stable blood pressure of 100/60, I.V. medication was stopped. Oral Gantrisin was continued for another week in a dosage of 8 to 12 gm. per day. During this period he developed an area of pneumonitis at the right base, for which he was treated with procaine penicillin, 600,000 units I.M. twice daily for 6 days. A normocytic normochromic anemia (hemoglobin 10 gm.) was treated with hematinics. The pneumonia cleared and 3 weeks after the start of therapy, the hemoglobin was 12

gm. However, convalescence was very slow. A persistent myocarditis was manifested by electrocardiographic changes, a high sedimentation rate, tachycardia at rest, and very poor exercise tolerance. The 17-ketosteroid excretion and the response of the circulating eosinophils to ACTH were normal during convalescence. It was felt that chronic adrenal insufficiency was not present. After a 6-months' convalescence, the patient was separated from the Service.

CASE 9. This 21-year-old white soldier with 3 weeks' service was admitted to the hospital on April 12, 1953, with a severe headache and nausea of 18 hours' duration. Past history was negative.

Physical examination revealed an acutely ill, drowsy male, with blood pressure 100/60, pulse 100 per minute, respirations 20, and temperature 106°. The pharynx was injected, and there was slight nuchal rigidity. There was a Grade III harsh systolic murmur heard over the pulmonic area, widely transmitted; the heart was not enlarged. The lungs were clear. The skin was covered with numerous petechiae, and several large confluent ecchymoses were present over the abdomen and thorax. The remainder of the examination was negative. Laboratory data included a spinal fluid pressure of 300 mm. with 114 cells per c.mm., of which 86% were neutrophils; Gram-negative diplococci on smear, which were later identified as Meningococcus Type II; 21,000 leukocytes per c.mm., of blood with 88% neutrophils, and 12% lymphocytes. The hemoglobin was 14 gm., and the urine was negative.

A diagnosis of meningococcal meningitis and septicemia was made and the patient was given 1,000,000 units of aqueous crystalline penicillin I.V., and 4 gm. of sodium sulfadiazine in 1 liter of 5% glucose solution I.V. following initial hydration with 500 ml. M/6 sodium lactate. The fever fell to 101°, and the murmur heard over the precordium diminished markedly in intensity. The patient felt well. Then 18 hours after treatment had been instituted, the blood pressure began to drop slowly to a level of 70/30; suddenly it became unobtainable. An I.V. infusion containing norepinephrine and aqueous adrenal extract was begun. The blood pressure could not be elevated above 50/0, and a transfusion of 500 ml. of compatible whole blood was given. During the next 12 hours the blood pressure fell to 0/0 on two occasions when the rate of infusion of norepinephrine and aqueous adrenal extract was decreased. The electrocardiogram showed a sinus tachycardia of 130, with inverted T waves and depressed R–ST segments in the precordial leads. Rales were heard at the right lung base. Oliguria and dyspnea became marked. An attempt at rigid fluid restriction was made, and congestive heart failure was treated with digitalis and oxygen inhalation. The problem of rigid fluid restriction was very difficult because with a decrease in the I.V. infusion rate of norepinephrine below a certain critical level the blood pressure would fall precipitously. During the first 36 hours of treatment the following quantities of medication were given: 18,000,000 units of aqueous crystalline penicillin I.M., 11 gm. of sulfadiazine I.V., 800 ml. of aqueous adrenal extract I.V., 20 ml. of lipoadrenal extract I.M., 500 ml. of compatible whole blood, 8 liters of I.V. fluids of which 2 liters were normal saline, 1,600 ml. were M/6 sodium lactate, and the remainder 5% glucose in water. With a blood sulfa level of 22 mg. per 100 ml. and marked oliguria, the administration of sulfadiazine was rigidly curtailed.

During the next 24 hours the patient improved and the blood pressure stabilized at a level of 96/60 following the discontinuation of norepinephrine and adrenal cortical steroids. The congestive heart failure steadily improved and on the fourth day of hospitalization a marked diuresis occurred. Inverted T waves noted in Leads 1, 2, aVL, and V3–V6 reverted to normal within 2 weeks. There were no clinical signs or laboratory evidence during the convalescent period which pointed toward a state of chronic adrenal insufficiency. Following a convalescence of 3 months, the patient returned to active military duty without ill-effect.

CASE 10. This 21-year-old white soldier with 2 month's service was well until the day of admission, May 19, 1953, when he noted the onset of headache, chills, fever, vomiting, and bloody diarrhea. Past history was negative.

Physical examination revealed an acutely ill, lethargic male with blood pressure 110/60, pulse 90 per minute, respirations 18, and temperature 101.6°. There was definite nuchal rigidity and a generalized purpuric eruption over the entire body; a few of these lesions were 1 cm. in diameter. The remainder of the examination was essentially negative. Laboratory data included an opalescent spinal fluid with 500 white cells per c.mm., of which 87% were neutrophils. Gram-negative intracellular diplococci were seen on smear, and were later identified from blood cultures as Meningococcus Type I. The leukocyte count was 28,200 per c.mm., with 93% neutrophils and 7% lymphocytes. Bleeding time,

clotting time, and blood platelets were normal.

He was given 1,000,000 units of aqueous crystalline penicillin and 4 gm. of sodium sulfadiazine I.V. initially, then aqueous crystalline penicillin, 1,000,000 units I.M. second hour and 2 gm. of sulfadiazine I.V. eighth hour. Soon after treatment had been started the blood pressure fell to 50/30. During the next 8 hours he received 40 ml. of aqueous adrenal extract I.V. and 2 ml. of lipoadrenal extract I.M. in addition to 1 liter of normal saline solution. The blood pressure, however, remained at shock levels until norepinephrine was started I.V. The blood pressure then rose to 100/50 and remained at normal levels following discontinuation of the norepinephrine 24 hours later. Convalescence was slow. The electrocardiogram showed a persistent right bundle branch block. There were no clinical signs of chronic adrenal insufficiency. The patient was returned to limited duty after a 2-month convalescent period.

Comments on Case Reports. In these 10 cases of meningococcal septicemia associated with shock there was a mortality rate of 50% despite the use of adrenal corticoids, norepinephrine, sulfonamides, and antibiotics. An analysis of these 10 cases reveals the following facts: 3 of the 5 fatalities occurred within less than 24 hours after the institution of therapy. In one patient, Case 5, death occurred 3½ hours after admission despite the use of what are considered adequate dosages of hydrocortisone, aqueous adrenal extract, norepinephrine, and sulfonamide (Gantrisin) intravenously; in this case, the blood pressure did not respond to the combined therapy. Case 1 in this group died 9 hours after the institution of therapy despite the use of Gantrisin, aqueous crystalline penicillin, cortisone, aqueous adrenal extract, and norepinephrine. The initial shock state was effectively combated with these drugs, but 6 hours later the blood pressure could no longer be kept above shock levels despite very large amounts of intravenous norepinephrine. Patient 4 died 22 hours after the institution of therapy with Gantrisin, cortisone, and aqueous adrenal extract. With the use of a whole blood transfusion of 500 ml. and the above medication, the blood pressure rose to normal limits without the use of norepinephrine. Subsequently, however, acute congestive heart failure developed with concomitant renal shut-down and the patient died 22 hours after admission. In each of these 3 cases massive adrenal hemorrhage was present as well as acute myocarditis and left ventricular failure. Gross vascular damage throughout the body was evident in these cases. Two of the fatalities (Cases 3 and 6) were delayed and occurred after the acute infection and initial vascular collapse had been controlled. Case 3 developed renal shut-down secondary to shock and sepsis. The acute adrenal insufficiency secondary to massive adrenal hemorrhage bilaterally, was successfully combated during the early phase. However, an early and precipitous rise in extracellular potassium occurred. With the use of blood dialysis this was alleviated, but with continuing anuria, extensive bronchopneumonia, and a severe degree of cerebral edema, the patient died on the seventh day. Patient 6 died in shock with acute myocarditis and left ventricular failure; considering the degree of myocardial damage present, the amount of intravenous fluid administered during the first 24 hours was somewhat excessive; namely 3,700 ml. of which 1 liter was physiological saline. However, the urinary output was good throughout this period. An extreme degree of hyperthermia, 106°, preceded the onset of congestive failure and vascular collapse, and it is tempting to speculate on whether damage to the autonomic nervous centers in the diencephalon and medulla may not have played a role in the production of pulmonary edema and vascular collapse; necropsy findings in the brain, however, were

minimal. Neither massive adrenal hemorrhage nor necrosis was present in Case 6, and, if shock was primarily adrenal in origin, it was due to acute functional adrenal insufficiency. The amount of adrenal hormone replacement therapy given to combat this was certainly large. Death was attributed to an acute myocarditis with left ventricular failure which did not respond to digitalis, phlebotomy, mercurial diuretics, and oxygen therapy.

Of the 5 patients who survived, 2 (Cases 7 and 8) had a residual myocarditis, which necessitated a prolonged convalescence and eventual separation from Army service. In one of these (Case 8), the only antibiotic used during the acute illness was Gantrisin. Norepinephrine did not prove necessary in the treatment of the acute hypotension, which was alleviated following the use of 50 ml. of aqueous adrenal extract I.V. In the other patient (Case 7) an acute myocarditis was present and the use of adrenocortical steroids probably helped to precipitate the acute congestive heart failure which occurred during the second day of treatment. Three liters of 5% glucose in water had been used intravenously during the first 36 hours of treatment; this amount of intravenous fluid was neither excessive nor causative in the production of congestive failure. In the 5 patients reported that have survived, there has been no evidence of chronic adrenal insufficiency. It is probable, therefore, that the surviving patients did not have massive adrenal hemorrhage with extensive destruction of glandular tissue, but rather an acute functional adrenal insufficiency.

Discussion. Meningococcal septicemia with shock is associated with a high mortality rate despite the use of modern adrenal hormone replacement therapy and antibiotics. The cause of shock and the sequence of events which often leads to an early death in this condition remain undetermined. Multiple factors are undoubtedly at work. Adrenal exhaustion, either functional or secondary to massive hemorrhage into the adrenal glands, is an important one. Other factors include toxic and destructive effects of the Meningococcus on the capillary and arteriolar vasculature, acute myocarditis, and central nervous system damage. Lesions in the central nervous system, however, need not be present to produce this clinical state, although in many cases there is an associated meningitis. In this series, 7 of the 10 cases had an associated meningitis. Acute adrenal insufficiency has been considered a most important element in this syndrome. Daniels[6], in his analysis of 300 fatal cases of meningococcic infection, found that of those cases with adrenal hemorrhage, the greater the degree of adrenal destruction found at necropsy, the shorter the clinical course. One is tempted to draw the inference from that study that the primary cause of shock in the so-called Waterhouse-Friderichsen syndrome is adrenal hemorrhage with resulting acute adrenal insufficiency. However, 30 patients (10% of the group analyzed by Daniels) died as a result of bacteremia without hemorrhage into the adrenal glands and with slight or no involvement of the meninges. In 22% of Daniels' cases, an acute myocarditis was found at necropsy. Ferguson and Chapman[8] state that there is often insufficient adrenal damage to explain the state of collapse. They believe that the ultimate cause of the peripheral vascular collapse seen in this condition is extensive vascular damage, resulting from direct bacterial invasion and the effect of meningococcal toxins on the blood vessel walls. Acute adrenal insufficiency and extensive cardiovascular damage are present in varying degree

in all of these cases; which factor is dominant in a given case is often impossible to ascertain clinically.

On the basis of our experience with this syndrome we would advise the use of the following drugs in its treatment. The dosages that follow are arbitrary. The combined use of aqueous crystalline penicillin and sulfonamide is advised. An initial dose of 1,000,000 units of aqueous crystalline penicillin intravenously followed by 1,000,000 units of aqueous crystalline penicillin intramuscularly every second hour is recommended. Either sulfadiazine or Gantrisin intravenously should be used concurrently. We prefer Gantrisin for the following reasons: it is highly soluble, it does not contain sodium ion, alkalizing salts are not necessary with its administration, and the very low incidence of hematuria and renal tubular blockage with its use offer distinct advantages in this syndrome which may be complicated by congestive heart failure and anuria. The following dosage is recommended: 4 gm. of Gantrisin in 500 ml. of 5% glucose in water as the initial dose, to be administered intravenously over a period of 1 hour, followed subsequently by 4 gm. of Gantrisin per 1,000 ml. of 5% glucose in water, to run at a rate which will give blood levels of free Gantrisin of between 10 and 15 mg. per 100 ml. We have found that between 10 and 18 gm. of intravenous Gantrisin per 24-hour period are necessary to produce such blood levels. A rigid restriction in the amount of intravenous fluid given during the first 24 to 36 hours of treatment is important. In general, no saline solution should be given, inasmuch as an acute myocarditis is a very frequent occurrence in this condition, and the concurrent administration of hydrocortisone and other adrenocortical substances may cause a retention of sodium and water of such magnitude as to precipitate acute congestive heart failure. Because of this high incidence of acute myocarditis and congestive failure, rapid digitalization with Lanatoside-C intravenously (1.2 to 1.6 mg.) is advisable as soon as the diagnosis is established. Water balance is a difficult problem to control inasmuch as the norepinephrine and hydrocortisone are conventionally administered by dilution in a large volume of fluid for intravenous use. To keep the fluid administered intravenously to a safe level of between 2,500 and 3,500 ml. per 24-hour period, the norepinephrine solution will have to be very concentrated. It is suggested that at least three 4-ml. ampules (24 mg. Levophed bitartrate) in 500 ml. of 5% glucose in water be administered intravenously rather than using one ampule in 1,000 ml. as is frequent current practice. Even higher concentrations are occasionally necessary to elevate the pressure above shock levels. An indwelling polyethylene catheter should be used to reduce the incidence of superficial sloughs. Next, 100 mg. of hydrocortisone should be administered by slow intravenous drip over a 6-hour period, diluted in 500 ml. of 5% glucose in water. Subsequently, intramuscular cortisone in a dosage of 50 mg. every 6 hours should be given during the critical phase of the illness. Aqueous adrenal cortical extract in a dosage of 30 ml. intravenously every hour may at times prove efficacious in critical cases. On two occasions we have noted in these acutely ill patients a marked bleeding tendency associated with a significantly elevated prothrombin time; this may have been a result of sulfonamide administration, bacterial damage to the liver, or other factors; Gantrisin reportedly does not elevate the prothrombin time (Pisciotta, Hinz and Hirschboeck[21]). Vitamin K intravenously may be beneficial in such circumstances;

this is speculative. However, in 2 of these cases a marked improvement in the prothrombin time was noted 24 hours after vitamin K administration. Transfusions of whole blood or plasma should not be given unless the acute hypotension is refractory to the therapy outlined. There is no deficit of plasma volume in these cases (Ebert and Stead[7]), and the use of transfusions will increase the potential danger of acute congestive heart failure.

The adrenal cortical steroids must be used cautiously. Salt and water retention may contribute significantly to the precipitation of acute congestive heart failure; this is a major problem in these patients whose hearts and kidneys are often extensively damaged. In addition, the over-all effects of these potent hormones in acute infectious states have not been clearly elucidated. The use of prednisone and prednisolone should be thoroughly investigated in this syndrome, since their salt and water retaining properties are considerably less than those of cortisone and hydrocortisone.

Early institution of therapy is essential, since a short delay in treatment may literally mean death. Aqueous crystalline penicillin and sulfonamide therapy, as outlined, should be instituted in acute septicemic cases as soon as the appropriate diagnostic tests have been done. The blood pressure should be checked every 15 to 30 minutes by trained personnel who are in constant attendance, since vascular collapse is often sudden and without warning.

Periodic determinations of the total circulating eosinophil count, as advised by Hodes, Moloschok and Markowitz[13], are of some value as a rough index of adrenal function. In 3 patients (Cases 1, 2 and 3) the initial eosinophil count was 60 cells per c.mm. or higher prior to therapy. With the administration of adrenal cortical hormones, the total circulating eosinophil count fell to zero. In Cases 5, 6 and 7 the eosinophil count was 0 per c.mm. from 2 to 10 hours prior to the onset of vascular collapse. Periodic eosinophil counts every 2 to 3 hours may have made recognition of impending acute adrenal insufficiency possible before the onset of vascular collapse. During the early convalescent period, a rise in total circulating eosinophils to high levels of 300 to 600 per c.mm. is not uncommon; this is a transient phenomenon. There has been no evidence of chronic adrenal insufficiency in any of the survivors, either clinically or by abnormal 17-ketosteroid excretion and eosinopenic response to ACTH (Thorne Test).

Conclusions. 1. Ten cases of acute meningococcic septicema with peripheral vascular collapse were treated at an Army Hospital during a 2-year period from 1953 to 1955. The mortality rate was 50% despite the use of antibiotics, sulfonamides, adrenal cortical replacement therapy, and norepinephrine.

2. Of the 5 patients who succumbed, 3 died in less than 24 hours after therapy had beeen instituted. All of these had massive adrenal hemorrhage as well as extensive vascular damage. One died 48 hours after admission from acute myocarditis with congestive heart failure and shock. Another died 7 days after treatment had been instituted, with extensive damage to the brain, cardiovascular system, kidneys, and adrenals.

3. Of the 5 patients who survived, 2 had protracted convalescence due to residuals of acute myocarditis, which is a major problem in a large proportion of these patients. In none of the survivors was there evidence of chronic adrenal insufficiency. Whether any case with massive adrenal hemorrhage can

survive is, therefore, an unanswered problem.

4. The concurrent use of aqueous crystalline penicillin and sulfonamides is strongly advised. When peripheral vascular collapse is present we have preferred to use Gantrisin rather than sulfadiazine. Hydrocortisone intravenously in a dosage of 100 mg. is recommended initially, followed by cortisone, 50 mg. every 6 hours intramuscularly. Occasionally, large amounts of aqueous adrenal extract intravenously have seemed of value. Extremely large amounts of norepinephrine are often needed to restore the blood pressure to normal; even then recurrent vascular collapse is a frequent occurrence.

5. Rigid restriction of salt and intravenous fluids is essential if acute congestive heart failure is to be avoided. The prevalence of acute myocarditis, generalized vascular damage, and the sodium retention incident to adrenal cortical hormone administration makes the occurrence of acute congestive heart a frequent complication in the treatment of this syndrome. For this reason the use of prednisone and prednisolone should be critically evaluated.

6. Despite all medications in current use and meticulous medical care, the mortality rate in this syndrome continues to be very high.

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CONCLUSIONES IN INTERLINGUA

Acute Meningococcemia con Collapso Vascular: Un Analyse de 10 Casos Recentemente Tractate

1. Dece casos de acute septicemia meningococcic con collapso del vasculos peripheric esseva tractate a un hospital del Armea durante un periodo de duo

annos inter 1953 e 1955. Le mortalitate esseva 50 pro cento in despecto del uso de antibioticos, sulfonamidos, norepinephrina, e therapia a reimplaciamento del substantias adrenocortical.

2. Inter le 5 patientes qui moriva, 3 moriva intra minus que 24 horas post le institution del therapia. Omne istes habeva massive hemorrhagia adrenal assi como extense damnos vascular. Un patiente moriva 48 horas post su admission, a causa de acute myocarditis con congestive disfallimento cardiac e choc. Un altere qui moriva 7 dies post le institution del tractamento habeva extense damnos al cerebro, systema cardiovascular, renes, e adrenales.

3. Inter le 5 patientes qui superviveva, 2 habeva convalescentias prolongate a causa de conditiones residual de acute myocarditis, lo que es un problema major de un grande parte de iste patientes, Nulle del superviventes monstrava indicios de chronic insufficientia adrenal. Si o non patientes con massive hemorrhagia adrenal pote superviver, es consequentemente un problema nondum solvite.

4. Nos urgentemente recommenda le uso concurrente de penicillina aquee crystallin e del sulfonamidos. In le presentia de collapso del vasculos peripheric nos ha preferite usar Gantrisina plus tosto que sulfadiazina. Le administration intravenose de hydrocortisona in un dosage de 100 mg es recommendabile al initio, sequite per cortisona in un dosage intramuscular de 50 mg omne 6 horas. A vices le administration intravenose de grande quantitates de aquee extracto adrenal pare esser de valor. Grandissime quantitates de norepinephrina es frequentemente necessari a restaurar le pression sanguinee al norma, e mesmo con isto recurrente collapso vascular es frequente.

5. Rigide restriction de sal e de fluidos intravenose es essential pro evitar acute disfallimento congestive del corde. Le frequentia de acute myocarditis, le generalisate damnos vascular, e le retention de natrium que accompania le administration del hormones adrenocortical face que acute disfallimento congestive del corde es un frequente complication in le tractamento de iste symptomas. Pro iste ration le uso de prednisona e de prednisolona debe esser criticamente evalutate.

6. In despecto de omne medicationes in uso currente e de meticulose tractamento medical, le mortalitate in iste syndrome continua esser multo alte.

PROGRESS
OF
MEDICAL SCIENCE

PEDIATRICS

UNDER THE CHARGE OF

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HEMATOLOGY OF LEAD POISONING IN CHILDHOOD

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THIS review of recent medical reports was prompted by the encountering in the past few months of two children who exhibited somewhat unusual hematologic expressions of lead poisoning. One exhibited a refractory anemia which lasted several months and the other had an episode of splenomegaly and acquired hemolytic anemia which did not subside until after hydrocortisone was given. On looking into the literature one finds surprisingly few accounts of the hematology of the disorder in children. Most of the current new work seems to be either in industrial toxicology or on the remarkable effects of therapy with chelates such as CaEDTA (calcium disodium ethylene diamine tetraacetate). Progress in the pathogenesis of the changes in the blood cells must wait for refinements in the technical procedures for measuring the minute quantities of lead which occur in the red cells, serum and tissues in lead poisoning; and must wait also for more detailed information in the general realm of red cell chemistry, particularly with respect to porphyrin metabolism, enzyme systems, and molecular architecture.

LEAD IN THE CIRCULATION. Once lead has been absorbed into the body, whether from the gastrointestinal or respiratory tracts or rarely from the skin, it is transported by the circulation and distributed to various parts of the body. As Aub, Fairhall, Minot and Reznikoff[1] (1925) pointed out, and as Cantarow and Trumper[3] emphasized in their more recent monograph (1944), in chronic poisoning the highest concentration of lead by weight is in the bones, lesser amounts in the liver and kidneys, and the lowest in the muscles,

heart, blood, lungs and brain. Lead is not stored very long in the soft tissues, but re-enters the circulation and is either excreted in the feces or urine or stored in the bones. The circulating and recirculating lead, as it comes in contact with the body tissues, gives rise to untoward symptoms when physiologic circumstances are favorable for this effect.

In the series of 54 children with lead poisoning reported by Deane, Heldrich and Bradley[4], the content of lead in whole blood ranged from 0.080 mg. to 0.730 mg. per 100 ml., and averaged 0.250 mg. per 100 ml. The blood level deemed maximal normal by most workers is in the neighborhood of 0.050 to 0.060 mg. per 100 ml., though occasional apparently normal adults without symptoms of lead poisoning have exhibited blood lead values up to 0.079 mg. per 100 ml. (Smith, Lewis and Wilson[21]). Top normal values for healthy children have not been clearly defined, but presumably are somewhat lower than with adults whose activities can bring them into more intimate daily contact with this industrial hazard. Most of the children with lead poisoning in our own experience have had blood lead levels in the range between 0.050 and 0.200 mg. per 100 ml.

Administration of CaEDTA therapy to an affected child is followed within a day or so by a moderate rise in the level of blood lead. By another day the urinary output of lead exhibits a pronounced increase (Bessman and Layne[2], Karpinski, Rieders and Girsh[13]). Both of these rises last only a few days despite continuation of therapy. It is believed that the calcium in the administered EDTA is replaced by the lead, and that the resultant PbEDTA complex is so stable that the contained Pb is nontoxic as it moves to the kidney.

Shipley, Scott and Blumberg[20] demonstrated that sufficient lead was present in the circulating blood of 9 children with lead poisoning to be detectable by spectographic analysis. Six normal children used as controls gave negative results or showed questionable traces.

The concentraion of lead per unit volume of blood at any one time bears no direct relationship to the severity of the symptoms being exhibited. Comparatively high concentrations may be found in individuals who are free of symptoms, and *vice versa*.

As far as can be determined, the reported analyses for the concentration of blood lead in affected children have been performed on specimens of whole blood. Actually, circulating lead is distributed between red cells and plasma in the proportion of 80% in the cells and 20% in the plasma[3]. Such an uneven distribution raises questions which cannot be answered as yet. For example: Can the concentration of lead in the red cells be viewed as approximately representative of the concentration in the soft structures of the body? Is the lead in the red cells combined with the stroma, or hemoglobin, or both? Is the amount in any single red cell held firmly, or will it be released if the concentration in the contiguous plasma is reduced? As for the lead in the plasma itself, is all of this free to injure structures with which it comes in contact, or has an appreciable fraction become relatively inert by being combined or "bound" to serum protein?

If the concentration of lead in plasma is the most important factor for inducing toxicity, then the comparative amounts of cells and plasma should be taken into consideration when evaluating the value for total blood lead. A child patient with a pronounced anemia will have a comparatively higher plasma content than another

child with the same total blood lead level but only a minimal anemia.

HEMOGLOBIN SYNTHESIS. A state of anemia may be said to be present in a patient when the hemoglobin level is below the range of values found in normal subjects of the same age (Wolman[23]). That children with lead poisoning are almost invariably anemic is so familiar a feature as to hardly require validating, but one may cite Ryan's[17] observations with 17 affected children. The hemoglobin values in these patients spread from 6.8 to 12.8 gm. per 100 ml., with a mean of 9.5 gm. The hematocrit values spread from 25 to 38% with a mean of 30%. Lower hemoglobin levels than Ryan's lowest reading are not infrequent.

The hemoglobin contained in each mature erythrocyte is formed inside the cytoplasm during the developing immature stage of that cell, while still nucleated. Biochemically, the intracellular synthesis of hemoglobin with molecular weight approximately 68,000 is the product of a myriad-phased series of atomic combinations and recombinations. The broader contours of this intricate process are being elucidated, but the detailed step-by-step sequences are still largely *terra incognita*.

To summarize sketchily, each hemoglobin molecule is composed of a strongly basic colorless histone protein complex known as *globin*, and a colored organic prosthetic complex known as *heme*[11]. Heme is a combination of ferrous iron with the protoporphyrin called protoporphyrin III. This latter substance contains the porphin nucleus and has 4 methyl groups ($-CH_3$), 2 vinyl groups ($-CH=CH_2$) and 2 propionic acid groups ($-CH_2CH_2COOH$) distributed along its periphery. The porphin nucleus consists of 4 pyrrole rings united in a ring by 4 methene linkages ($=CH-$). Each pyrrole ring contains 4 carbon and 1 nitrogen atom.

Synthesis of pyrrole appears to begin within the Krebs citric acid cycle, where acetate is built up to 2-ketoglutonic acid ($COOH.CH_2.CH_2.CO.COOH$). Two of these latter molecules join up with one of glycine to form pyrrole. This in turn goes through an intricate series of steps, including decarboxylation and condensations, to end up as protoporphyrin III. During this process, minimal quantities of other porphyrins known as coproporphyrin I and III and uroporphyrin I and III are also formed.

The total *quantitative* rate of production of hemoglobin is retarded, manifesting itself as anemia, but the qualitative character of the hemoglobin is unaltered. It is normal adult or "A" hemoglobin entirely in lead poisoning.

The protoporphyrin which accumulates in the red cells is almost entirely protoporphyrin III, a normal hemoglobin precursor. Normal red cells always contain a little protoporphyrin III in their stroma, approximately 13 mcg. per 100 ml. (Schwartz and Wikoff[18]). In lead poisoning this intracellular constituent becomes much increased, often to 500 mcg. per 100 ml., or higher. From this and related observations in other anemias it is believed that this excess of erythrocyte protoporphyrin reflects interference in higher synthesis, perhaps in the conversion of newly formed protoporphyrin into heme[18].

Quantitative studies of the blood and urinary porphyrins in lead workers by Kench, Gillam and Lane[14] have shown that the content of protoporphyrin in blood and urine during lead poisoning is very much less than would be the case if its presence were the result of overflow from erythroblastic protoporphyrin whose intracellular union with iron had been blocked. These authors found no correlation between the protoporphyrin content of the blood

and either the lead content or the number of stippled red cells.

Some young cells may contain sufficient protoporphyrin to exhibit fluorescence when viewed microscopically under ultraviolet light ("fluorescytes"). This microfluorescence is detectable most prominently in the primitive red cells, but may also be seen in the reticuloendothelial cells, myeloid cells and bony structure of the bone marrow (Vannotti and Delachaux[22]). The kidney, liver and other organs show no increase in porphyrin content.

Duck erythrocytes and immature mammalian erythrocytes under appropriate circumstances can synthesize heme *in vitro*. Eriksen applied this procedure to the problem of the effect of lead on biosynthesis[7]. Traces of lead inhibited the *in vitro* production of heme, apparently as the result of diminished intracellular formation of porphyrin.

Vannotti and Delachaux[22] noted that after hemolysis produced by phenylhydrazine, both humans and animals with lead poisoning showed serum iron curves which rose to much higher levels and remained elevated longer than the corresponding curves of normal controls. This, other experiments with reticuloendothelial blockade, and the familiar observation that tissue hemosiderosis is prominent in lead poisoning, support the hypothesis that the utilization of iron is hampered.

ERYTHROCYTES. Typically, both the red cell count and the hemoglobin level are depressed if the lead poisoning is sufficient to produce symptoms in a child. The red cell count as a rule is less depressed than the hemoglobin level, producing a "hypochromic" picture in the blood smear. Other morphologic distortions evident in the smear are anisocytosis (lack of uniform size) and poikilocytosis (bizarre shapes). Stippling, another frequent feature, is discussed in the next section.

Reticulocytes are increased as a rule. These usually represent 1 to 2% of all the circulating red cells (normal for children, 0.5 to 0.9%). Reticulocyte counts up to 5.0% are encountered occasionally, and rarely may be higher.

STIPPLING. Basophilic rounded granules, within the red cells in lead poisoning are usually but not always present. Giannattasio, Bedo and Pirozzi[10] reported between 1,500 and 17,000 stippled forms per million red cells (0.15 to 1.7%) in 9 of 14 affected children; the remainder were listed as having "no stippling."

These granules are believed to be cytoplasmic residues, containing or consisting of products of incomplete hemoglobin production. Their size is variable. The largest ones occur in small distorted achromic cells whose stroma clearly has been poorly formed (McFadzean and Davis[15]). The presence of ribonucleic acid in their substance has been suggested by the histochemical studies of Dustin[6]. Stainable iron occurs in the larger granules[15].

McFadzean and Davis[15] noted that basophilic stippling may be seen in developing red cells within the marrow, but only in normoblasts and polychrome erythrocytes whose staining qualities demonstrate that hemoglobin is being, or has been, formed. The marrow may exhibit large reticuloendothelial cells which contain phagocytized erythrocytes and basophilic granular masses. Such observations suggest that stippling is the result of faulty erythrogenesis in the bone marrow, rather than the direct effect of lead upon the mature red cells released to the circulation.

In guinea pigs poisoned with lead, McFadzean and Davis noted that the proportion of circulating stippled cells, including cells whose granules gave a positive iron reaction, became much

enhanced after splenectomy. The animals so operated on also had an amelioration of their anemia. The spleen in these animals was 2 to 5 times normal size, and on histologic study showed pulp engorgement, hemosiderosis, and reticuloendothelial proliferation. The conclusion may be drawn that the spleen in lead poisoning removes preferentially the more defective red cells.

Thus the pathogenesis of anemia in lead poisoning is the consequence of both (a) defective hemoglobin production, and (b) accelerated destruction of abnormal red cells by the spleen and presumbaly by the reticuloendothelial system as well.

SIDEROBLASTS AND SIDEROCYTES. Small particles of nonhemoglobin iron, stainable with the potassium ferrocyanide-hydrochloric acid technique, occur in lead poisoning in great abundance, inside both the mature erythrocytes ("siderocytes") and the normoblasts ("sideroblasts"). As a rule these iron-staining granules are not apparent in blood films stained with Wright's or other Romanowsky stains. The more severe the lead intoxication and the larger the granules, the higher the proportion which give a positive iron reaction[15]. Not all the stippled cells so prominent in lead poisoning are siderocytes in terms of the above definition. In 8 cases of lead poisoning studied by Kaplan, Zuelzer and Mouriquand[12], the sideroblasts represented 50 to 100% of all marrow normoblasts (the proportion of siderocytes to circulating erythrocytes is not stated). Conversely, infants and children with hypochromic iron deficiency anemia had a diminished incidence of sideroblasts, usually less than 1%. These authors, and also Douglas and Dacie[5] who have made similar observations, indicate that stainable nonhemoglobin iron granules in normoblasts is a normal phenomenon. This iron presumably is destined to be utilized in the process of hemoglobin maturation. In health these granules disappear at the reticulyte stage or earlier.

Sideroblasts in the marrow in appreciable numbers have been described in normal children and children with diverse forms of anemia such as megaloblastic anemia, thalassemia major and hemolytic anemias[5,12]. As stated, in normal subjects who have sideroblasts in the marrow, the peripherally circulating erythrocytes are as a rule free from iron granules. Siderocytes have been described in erythroblastosis fetalis, atypical congenital hemolytic anemia, phenylhydrazine poisoning, uremia and myelosclerosis[5,12]. After splenectomy, siderocytes become more abundant.

OTHER HEMATOLOGIC FINDINGS. Studies of red cell osmotic fragility in a graded series of hypotonic saline solutions have received little formal attention. Fullerton[9] found, in 8 men with chronic lead poisoning, a consistently diminished fragility (increased resistance) of varying degree.

The bone marrow is typically within normal morphologic limits, apart from the stippling, but sometimes shows a normoblastic hypercellularity[9].

A leukocytosis is sometimes evident during a period of acute symptoms. Deane, Heldrich and Bradley[4] noted in 54 children a spread from 5,000 to 27,000 in total count, with an average of 16,310. Giannattasio, Bedo and Pirozzi[10] in 14 children noted a spread from 5,700 to 30,000, with an average of 12,500. In the latter group one child had 5% and another 10% eosinophils; most of the remainder were described as showing "no eosinophils." Morphologic alterations in the appearance of the circulating granulocytes are evidently uncommon, though toxic granules may be seen in the cytoplasm of some of these cells.

Cantarow and Trumper[3] (1944), who

have surveyed the older literature dealing with lead poisoning in adults, comment that leukocytosis is infrequent. They cite several reports of an increase in monocytes or lymphocytes, and of an occasional eosinophilia. There may be an increase in the relative number of young granulocytes, and even myelocytes may appear in the blood stream. Ferguson and Ferguson[8] (1934) are quoted as noting that immature granulocytes are more abundant in acute poisoning and hypermature granulocytes in chronic poisoning. Shiels[19] (1954) has reported that exposure of adult workers to lead results in an increase in the differential count, in the proportion of large lymphocytes to small lymphocytes, and in the ratio of the total of large lymphocytes and monocytes to small lymphocytes.

Platelets are usually normal in numbers but may be decreased. Coagulation defects are rare if they occur at all.

McGovern and Simmons[16] (1950) have described a 2-year-old patient who exhibited a persistent eosinophilia, fluctuating between 7 and 20% of all leukocytes, and a firm large spleen. They comment that a bibliographic survey failed to reveal any other recorded case of lead poisoning with associated eosinophilia and splenomegaly.

Summary. The predominant hematologic lesion of lead poisoning is the faulty production of red cells and hemoglobin. The developing immature erythrocyte of the marrow is clearly much more susceptible to the noxious action of this intracellular poison than are the other marrow cells. The lead appears to depress the conversion of protoporphyrin into heme, and to hamper the formation of stroma in some of the red cells. It has not been feasible from the recorded childhood cases to derive any generalizations with respect to significant relations between the severity of the blood changes, the level of blood lead in random test specimens, the age of the patients, the duration of exposure, or the intensity or character of the constitutional symptoms exhibited.

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SUMMARIO IN INTERLINGUA

(See page 629 for original article)

Observationes Clinic Super 712 Casos de Tetano Subjicite a Quatro Diverse Methodos de Tractamento. Mortalitate de 18,2 pro Cento sub un Nove Methodo de Tractamento

Tetano es frequente in Brasil. Durante le dece annos 1944–1954, 692 casos esseva admittite al Hospital das Clinicas. Sub le "vetere" regime therapeutic de sedation e sero antitetanic le mortalitate esseva 27,2 pro cento.

Un "moderne" regime de continue administration intravenose de Mephenesina (3-ortho-toloxy-1,2-propanediol), sedation supplementari de barbituratos o hydrato chloral, antibioticos, alimentation intravenose, e parve doses de antitoxina (100.000 U.I.), esseva administrate per infirmeras specialmente trainate. Iste therapia, empleate depost 1952, ha reducite a 18,2 pro cento le mortalitate del ultime 236 casos consecutive. Hibernation inducite per drogas, que esseva addite a iste regime in 21 casos, resultava in elevar le mortalitate a 52,3 pro cento, e consequentemente es recommendabile solmente pro le pauc patientes con reactiones emotional exaggerate.

Crises apneic require attention special con constante observation pro lor detection e tractamento durante le prime 15 secundas del episodio. Tal crises generalmente responde a un augmento immediate in le administration intravenose de Mephenesina usque le fin del episodio.

SUMMARIO IN INTERLINGUA

(See page 648 for original article)

Mesuration del Eventos Mechanic e Electric in le Cycle Cardiac I. Effecto de Tachycardia, Medication Pre-Anesthetic, e Anesthesia a Ethere Diethylic

Esseva studiate in humanos le relationes temporal registrate in le electrocardiogramma, le phonocardiogramma, e in registrationes del pulso del arteria carotide sub conditiones de variante frequentia cardiac e anesthesia a ethere. Le intervallos ab le initio del complexo QRS usque al initio del prime sono cardiac e le ascendita del unda del pulso del arteria carotide e ab le prime sono e le initio del ascendita del unda del pulso del arteria carotide usque al initio del secunde tono esseva relationate a cambiamentos in le frequentia cardiac.

2. Acceleration cardiac regularmente produceva accurtamento del periodo isometric, indirectemente mesurate, del ventriculo sinistre, in grande parte a causa del accurtamento de su phase mechanic.

3. Le resultatos obtenite durante profunde anesthesia a ethere esseva considerate como indicios que iste typo de anesthesia produceva un inhibition del frequentia del eventos e electric e mechanic intra le myocardio.

4. Le technica empleate pare presentar un medio sensibile pro le studio de certe aspectos dynamic del action cardiac. Illo pare haber un valor special in le evalutation de procedimentos o de drogas quando altere medios de studio non es usabile.

GYNECOLOGY AND OBSTETRICS

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NONOBSTETRIC SURGICAL COMPLICATIONS DURING OBSTETRIC CARE: A REVIEW OF THE RECENT LITERATURE

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FOR the purpose of organized presentation, the subject is divided into the complications of intragenital and those of extragenital origin. The intragenital complications are apportioned into those of the lower genital tract and those of the upper tract. The extragenital ones are subdivided into three brackets: head, neck and thorax, abdomen and miscellaneous areas.

THE LOWER GENITAL TRACT. Here the pathologic developments may be minor in gravity but their frequency demands consideration. Except for malignancy, corrective procedures for these conditions have been deferred during pregnancy.

Vulvar condylomata acuminata thrive on the increased moisture and turgescence that is a part of the normal pregnancy changes in this area. Their incidence is around 1:200[120]. The diagnosis is made by inspection, as a rule, but in case of doubt, microscopic examination of excised tissue is indicated. The treatment consists of the local application of 25% podophyllin ointment or electrosurgical excision and coagulation[43,182]. Extreme vascularity may make it wise to defer definitive treatment until pregnancy is terminated. Excessive growth of the condylomatous masses, that are always the seat of secondary infection, may necessitate Cesarean section[178]. Other benign growths of the vulva are lipomata, hidradenomata and papillomata. The excision of these is best deferred until termination of the pregnancy unless they produce symptoms that require surgical intervention. Carcinoma of the vulva is exceedingly rare in the childbearing age. While no concomitant instance has been reported recently, the

vaginal delivery of a patient after radical operation for this condition was reported by Rubin and Lewis[157]. The Bartholin glands become infected during pregnancy occasionally, with abscess formation that requires drainage or possibly complete excision[43,149,178]. The chance of puerperal infection or the possibility of infant infection, particularly the eyes, from rupture during delivery is eliminated by prompt surgical care[182]. Bartholin gland cysts, unless they reach an exceptional size interfering with delivery, should remain untouched during pregnancy. Vulvar varicosities enlarge progressively from conception to delivery and recede following parturition or when the fetus dies *in utero*[82]. During pregnancy, they may attain such proportions as to cause a great sensation of weight and considerable discomfort. The desire to relieve the patient's discomfort may lead to measures that only aggravate the situation[43]. Sclerosing injections often result in painful phlebitis and the best treatment is general medical care with patience until the delivery leads to remission[82,107,182].

Since the vaginal wall is not provided with secretory glands, cysts that develop in this area are either congenital in origin or due to the inclusion of foreign matter. Gartner's duct cysts, the congenital type, are located at the junction of the lateral and anterior vaginal walls. The inclusion cysts may develop at any site of previous trauma. They rarely become infected or undergo malignant change and usually accommodate themselves to vaginal delivery. Should one become too large during pregnancy, it should be aspirated or excised prior to the last trimester[43,107,120,167,178].

Both cervical atresia and stenosis are rare complications of pregnancy, because of the difficulty of conception. The etiology includes congenital aberrations, therapeutic procedures for cervicitis, attempted abortion and healing following severe cervical laceration. The treatment depends upon the degree of cicatrix and stenosis. Usually, the normal softening of the genital structures permits gradual dilatation but an unyielding cervix during labor may require Cesarean section[181]. Cervical polyps are common during pregnancy and cervical myomata are unusual. They should be unmolested unless they give rise to bleeding or to the question of malignancy. Under these circumstances, excision with careful attention to hemostasis and subsequent pathological examination is indicated[182].

The management of cervical cancer complicated by pregnancy has aroused opinions that are varied and recommendations that are conflicting[43,54,67,76,86,105,116,167,180,198]. For the purpose of clarity, the extent of disease in cervical cancer is denoted by stages from 0, meaning confined to the mucosa, through stages I, II, III, and IV, as the disease progresses to widespread involvement of the pelvic viscera and probable distant metastasis. The stages of pregnancy, meaning the maturity of the fetus, are denoted by the terms *previable:* up to 20 weeks gestation and *viable:* between 20 weeks and delivery. The majority of early carcinomas, stages 0 and I, are diagnosed not because of symptoms but as a result of visual examinations of the cervix followed by cytologic smear and biopsy of suspicious lesions. Attention may be called to these lesions by the single symptom of vaginal staining which should always indicate a careful vaginal examination regardless of the stage of pregnancy[109,198]. Invasive cervical cancer is a rare complication in pregnancy because the malignancy hinders fertilization, increases abortion and interferes with normal uterine growth[43,67].

A collected incidence of 0.8% in 122,800 deliveries has been reported[76,198]. In smaller series, the incidence of 0.27% to 0.59% was found[86,149,180]. The common delay in diagnosis is due to the frequent ill-advised reluctance of the physician to conduct a speculum examination during pregnancy despite the presence of bleeding[109].

In regard to stage 0 cervical cancer, considerable has been written concerning the cytologic and microscopic similarity between the alterations in malignancy and the normal histologic changes that occur as a result of pregnancy[66,111,126]. Diagnosis with positive exclusion of the pregnancy changes and conclusive elimination of microscopic invasion is of first importance. This may be done by microscopic study of liberal cold knife biopsy material by a competent pathologist[66]. In the absence of microscopic invasion, simple electrothermic conization is adequate therapy, provided the patient is closely followed by repeat cytologic studies, vaginal examinations and biopsy when indicated. Following delivery, the problem should be re-evaluated at the end of 6 to 8 weeks by smears, cervical examination and biopsy. Persistence of intra-epithelial change will indicate either wider cervical conization, amputation, or hysterectomy. Microscopic evidence of invasion would place the lesion in stage I with the attendant requirement for either radical surgical or radical irradiation therapy.

With invasive cancer, if irradiation is the treatment of choice, its effect on the fetus is an important factor, for no such pregnancy should be permitted to go to term[63]. When administered prior to the 26th week, irradiation yields a very high percentage of microcephalic infants unless the pregnancy is terminated[43,63,67]. Vaginal delivery is dangerous for both mother and infant because the neoplastic tissue increases the risk of hemorrhage, laceration and cervical dystocia[21]. Furthermore, the trauma of vaginal delivery or premature expulsion may well incite rapid extension. While the literature favors irradiation over radical surgery, the choice of treatment should be guided by the stage of disease and the stage of the pregnancy.

In stages I and II of cervical cancer during the previable stage of pregnancy, the chief concern should be the welfare of the mother. Any appreciable delay in therapy might well decrease the mother's chances for survival[67,75,159,163,198]. Roentgen-ray therapy will usually cause abortion in three weeks[159]. If spontaneous abortion does not occur, a hysterotomy or dilatation and evacution should be performed[43,54]. Many feel that the products of conception should not be extruded or removed through a carcinomatous cervix no matter how early the pregnancy, and hysterotomy followed by irradiation is strongly advocated by Johnson[86] and Finn[54]. Other programs of therapy include: 1) Radical hysterectomy[76,101,116]. 2) Wertheim hysterectomy followed by irradiation[105]. 3) Supracervical hysterectomy and bilateral salpingo-oöphorectomy with subsequent radium and external irradiation[67,76]. 4) Hysterotomy, deep irradiation, radium and radical hysterectomy 6 weeks to 3 months later[86].

With the fetus in the stage of viability (20 weeks or more gestation) the infant should be considered and the pregnancy allowed to continue to the approximate time of expected maturity. Cesarean section is the chosen method of delivery in order to avoid cervical trauma, hemorrhage and malignant dissemination[7,43,54,75,105,116,159]. The Porro hysterectomy followed by postoperative irradiation is recommended by some[67,75,76,86,105]. Cesarean section followed by radical hysterectomy has been sug-

gested but the great pelvic vascularity is a deterring factor[76,101]. Those who advocate irradiation therapy for cervical carcinoma feel that the presence of the corpus aids in the radium therapy, by reducing the bowel and bladder complications[159,163,198]. If the cervical lesion proves to be radio-resistant, as indicated by clinical biopsy and cytologic study, subsequent radical surgery should be utilized[116,163].

For stages III and IV of cervical cancer with a previable infant, particularly in the first trimester of pregnancy, Roentgen-irradiation followed by spontaneous abortion is recommended by some[86,105,116]. The wisdom of this is questionable because of the necessary dilatation of the cervix that attends the abortion. Abdominal hysterotomy followed by Roentgen-irradiation and the subsequent local application of radium is preferred. In the most advanced stage of cervical cancer, the pregnancy may be permitted to continue unmolested, in the fetal interest, since the mother can be afforded palliation only. With a viable infant, the child should be permitted to grow to approximate maturity and delivered by Cesarean section. Subsequent treatment consists of external irradiation first, to be followed by the intracavitary and intravaginal use of radium[43,54,76,105,159,163]. Total exenteration or some modification of radical pelvic surgery may be done later, depending upon individual circumstances[116].

The treatment of the pregnant patient with cervical carcinoma has always been a complex problem and the complexity has been increased by the revitalization of radical surgery for cervical cancer. Several conclusions may be drawn. The presence of cervical cancer contraindicates vaginal delivery of a sizable fetus and indeed of any fetus in the minds of some. Preservation of the uterine corpus aids in reducing the complications of irradiation therapy. This is contraindicated if preservation of the fetus is anticipated. Pregnancy should not alter the prognosis of cervical carcinoma except for the delay in diagnosis and therapy that frequently accompanies this combination[21,109].

THE UPPER GENITAL TRACT. In general, the complications of the upper genital tract demand more diagnostic acumen and surgical skill than do those of the lower tract. Here, the lesions cannot be visualized and the procedures are major in scope. The incidence of operations for the sole purpose of diagnosis involving the upper genital tract is 0.1% to 0.3%[28,149].

The presence of congenital uterine anomalies are quoted to vary from 0.07% to 0.15%[52,169,176]. Normal fertility may exist but the abortion risk is four times the average rate. Antepartum complications, such as hemorrhage, malpresentation, premature rupture of membranes and surgical operations, are markedly higher. Intrapartum uterine inertia, operative deliveries and postpartum hemorrhage are above the average rate. Most surgical complications are found in the presence of duplication, notably the bicornate uterus. The nonpregnant horn may become incarcerated, with symptoms of an acute abdominal catastrophe[52,176]. Occasionally, a suspected ectopic pregnancy may prove to be an intrauterine pregnancy in a septate uterus. The incidence of Cesarean section in these patients should be higher than normal to avoid complicated vaginal deliveries with increased fetal mortality[52,176].

In the consideration of myomata in pregnancy, a review of the anatomy and physiology of the tumor is essential before management is discussed. The myoma is a fleshy, parasitic tumor. Its only blood vessels are arteries, arterioles and capillaries, for the veins do not

penetrate the tumor. The beds of capillaries empty into the veins, which are concentrated about the periphery of the tumor. A single nutrient artery frequently nourishes a myoma. The demands of the tumor may exceed the capacity of the arteries, with resulting degeneration. Red or carneous degeneration of a uterine myoma consists of hemorrhagic infarction in a previously hyalinized myoma. The hemorrhage probably results from venous obstruction with concomitant rupture of the thin-walled arteries. Blood is pumped into the tumor and it cannot escape. This concept explains the rapid swelling, tenseness, edema, and the uniform coloration and leads to logical treatment[49,150]. Pregnancy does not stimulate the growth of myomas. There is no evidence of muscle hypertrophy or connective tissue hyperplasia. The alleged enlargement is more apparent than real, and largely due to the rise of the uterus out of the pelvis. Any tumor enlargement is due to edema usually from benign degeneration. This appears in 50 to 70% of myomas in pregnancy compared with 7.8% in the nonpregnant state[136,150].

Myomata affect pregnancy in many ways, with a reported incidence of 0.3% to 7.2%[60,64,136]. Productive fertility is reduced 7 to 17% by tubal obstruction, and by intra-cavitary distortion with faulty implantation. Abortions are twice the usual frequency. Myomas increase fetal malposition, uterine inertia, obstructive dystocia, premature labors and postpartum hemorrhage[60,107,136,156,167,199]. In addition to the above complications, uterine myomata during pregnancy are subject to changes that may raise the question as to the wisdom of removal of the tumor in the effort to retain the pregnancy. These tumors rarely become infected or gangrenous and when treated expectantly, the symptoms usually subside[49,72,136]. Myomectomy may be indicated for severe pain that does not subside under palliative management. The tumor with acute degeneration, infection, or gangrene demands surgical removal[36,67,150]. The procedure requires minimal uterine manipulation and the uterine incision should be so made as to avoid the cornual angles and the large vessels. The complications following myomectomy during pregnancy, particularly that of abortion, have served as a deterrent against this procedure. The abortion incidence after myomectomy during pregnancy is quoted as 34.3% by Davids[36], 54% by Childs[28], and 42% by Roques[156]. Furthermore, the danger of socket hematoma and pelvic phlebitis is much greater than in the nonpregnant state. For these reasons, the statement, "We have ample reason for folding our surgical hands until term approaches"[156], is valid. In the care of patients with myomata, as term approaches, a sterile vaginal examination should be done to make sure that the birth passage is clear. In the event of tumor previa, unless the tumor can be pushed out of the true pelvis, Cesarean section is indicated. At the time of the Cesarean section, myomectomy should not be undertaken unless the tumor is pedunculated and the pedicle is small[136,150,156].

The management of the patient who has had a myomectomy raises the question as to the best mode of delivery. Davids[36] reported a series of 153 myomectomies that involved the endometrial cavity without a ruptured uterus. The patients were delivered by either Cesarean section or by the vaginal route. The details are not listed. On the other hand, 35 incidences of post-myomectomy rupture during pregnancy or labor were reported by Pedowitz[137]. He concluded that the operative note of myomectomy should always indicate the extent and the depth of the incision

particularly in relation to the uterine cavity. He recommends Cesarean section in the event of entrance into the endometrial cavity or of a febrile postmyomectomy course. In summary, a myomectomy is rarely indicated during pregnancy except for tumors with infection or torsion and gangrene. The procedure is followed by a very high abortion rate and may be followed by socket hematoma or pelvic thrombophlebitis. The best policy is that of symptomatic treatment until time of delivery. At this time, the method of delivery should be individualized with complete awareness of the problems of sterility, inertia, malpresentation, and the previous surgical history.

Malignancy of the uterine corpus in the childbearing age is infrequent and with superimposed pregnancy it is extremely rare. Carcinoma or sarcoma of the corpus uteri during pregnancy is reported in the world's literature[74,129,174].

Torsion of the human pregnant uterus is reported 108 times in the literature, according to Nesbitt[128]. This entity is associated with allied pelvic pathology in 80% of the cases. The picture of pain to the point of shock in a gravid patient should suggest this possibility especially in the presence of known myomas, congenital abnormalities, intestinal adhesions or ovarian cysts. The greatest error is in mistaking torsion for a nonsurgical condition. The treatment is an emergency laparotomy, detorsion, and whatever pelvic surgery that is immediately mandatory[128]. If the fetus is near term, Cesarean section is prudent.

Gunshot wounds of the abdomen are not uncommon. The mortality of penetrating wounds is between 48 and 61%[154,196]. The frequency of uterine injury is low but as gestation nears term the chance increases. Abdominal tenderness and rigidity are the most valuable diagnostic signs of perforation. All instances of perforating abdominal wounds require immediate surgery with particular attention to the pregnant uterus as well as to the intestinal tract. Wilkinson[196] states that shock is no contraindication to operation but our judgment suggests that it would be better to stabilize the patient before the beginning of the surgical procedure. Treatment of a perforated uterus depends upon the maternal, fetal and uterine conditions. Kobak[91] states that if the fetus is dead or at a previable age and if the perforation is small this should be repaired and spontaneous vaginal delivery planned. Extensive uterine damage, however, necessitates Cesarean section and hysterectomy. If the fetus is alive, and at a viable age, Cesarean section is indicated with immediate hysterectomy if the uterine wall is badly damaged. When the maternal condition is precarious, it is best to suture the perforation and close the abdomen but in case the mother is moribund a viable fetus should be removed with great speed. The mortality rate is quoted as 55% for the fetus and 9% for the mother[91]. Obviously, this is an acute emergency that demands urgent therapy and well-organized teamwork.

Surgical complications that involve the fallopian tubes during pregnancy are not common. Instances of rupture of a tubo-ovarian abscess have been recorded by Lowrie[103] and by McCall[107], although these may have been ruptures of infected ovarian cysts. Lowrie[103] reported an instance of torsion with gangrene of a pyosalpinx. Blum[17] found that 12% of 201 cases of torsion of the salpinx occurred during pregnancy. He also pointed out that this accident is associated with such tubal disease as hydrosalpinx, pyosalpinx, hematosalpinx or tumor usually. This observation was confirmed by

Eastman[12], Anspach[3] and Kushner[97]. Nevertheless, instances of torsion of the normal tube have been recorded by Caldwell[24] and Stark[171]. The possibility of this accident arises in all instances of acute lower abdominal catastrophe that are associated with severe pelvic pain, nausea and vomiting, acceleration of the pulse with a normal or slightly elevated temperature. A tender mass may be palpated lateral to the uterus[17]. The treatment is immediate operation with removal of the gangrenous tube and possibly the ovary. The decision as to the infant will depend upon whether or not viability has been attained. In the previable phase of pregnancy, the abdomen should be closed and normal delivery anticipated.

The incidence of ovarian complications in pregnancy that require surgical intervention is reported to vary from 1:80 to 1:1,000[68,71,156]. As a rule, these complications are associated with ovarian tumors. These tumors may be divided into two large classifications: the nonproliferative and proliferative. The former enlargements are benign and include graffian follicle cysts, corpus luteum cysts, follicular cysts, tuboovarian cysts and theca luteum cysts. They do not become malignant but are subject to the other accidents that may occur to all ovarian tumors. The proliferative tumors are divided according to tissue into epithelial, embryonic, connective tissue, and those of metastatic origin[130]. In addition to the accident hazard, these tumors possess the potentiality of malignant transformation. Solid ovarian tumors have a much higher incidence of complication than do the cystic ones. According to Dougherty[41], 75% of the solid tumors developed such complications. Of equal importance are the cystadenomata with a high potential for both accidents and malignant transformation. The solid sex-cell tumors have also been reported during pregnancy[38,48,69,90,200]. Dougherty[41] makes a point that the basic quandary is difficulty in distinguishing solid from cystic tumors. Of the cystic tumors, 25% are dermoid cysts[47]. These cysts are prone to torsion and gangrene as well as to infection or rupture with dissemination of their contents throughout the pelvic peritoneal cavity[41,142].

The ovarian tumor is best diagnosed in early pregnancy when the enlarged uterus does not interfere with adequate pelvic examination. The discovery of a small freely movable cyst with no areas of firmness indicates expectant observation. Cysts that are larger than 6 cm. in diameter should be removed, as should those with nodules, and all solid tumors[41,46,67,68,70,72,149,156,167].

The time of removal of ovarian tumors complicating pregnancy has been the subject of considerable discussion. In the presence of an acute accident, such as torsion with gangrene, infection, intracystic hemorrhage or suspected malignancy, immediate operation should be undertaken regardless of the stage of gestation[20]. On the other hand, with an ovarian tumor that requires only deliberate action, the present consensus is that its removal should be deferred until the middle trimester of pregnancy, following transfer of endocrinal function from the ovaries to the placenta. At the time of removal, great care should be taken not to disturb the uterus and to obtain complete hemostasis. If removal is done during the second trimester, sacrifice of the corpus luteum does not seem to increase the incidence of abortion[18,28,47,70].

Excision of, or injury to, the corpus luteum prior to this time indicates postoperative hormone therapy[47,71]. Retention of the pregnancy following removal of the corpus luteum has been reported by Grimes[68] and Bonn[18] even

in the first trimester of pregnancy. In contrast to the high abortion rate following myomectomy, this rate following oöphorectomy is not disturbing. Randall's[149] series of 10 cases resulted in no abortion and the highest percentage of postoperative abortion was reported by Childs[28] as 21%. Other recorded figures are: 2.5%[142], 6.8%[156], 19%[167]. The abortion incidence increases with the preponderance of operations that are performed during the first trimester, and McKerron[112] demonstrated that laparotomies done in the 13th to 20th week of gestation are followed by the lowest abortion rate[70,71,156].

The sword that hangs over the obstetrician who is waiting to remove the ovarian cyst is double-edged: the danger of an acute accident which could be recognized readily and the possibility of malignant transformation which may not be recognized early enough. According to Randall[149], 5% of the ovarian tumors that he removed during pregnancy showed malignant transformation and this figure raises the question as to whether ovarian tumors that require removal should be excised immediately after diagnosis, instead of at the optimal theoretic time as to the pregnancy. In a report on endometriosis and pregnancy, Scott[166] pointed out the possibility of rupture of an endometrial cyst, particularly during labor. While it is unusual, the patients with extensive endometriosis do become pregnant. It is well-known that endocrinal changes during pregnancy result in regression of the endometriosis but this is not true of the large chocolate cysts of the ovaries. Therefore, the diagnosis of endometriosis with ovarian enlargement concomitant with pregnancy indicates that the cyst should be treated as any other ovarian cyst, namely surgical removal during the second trimester[166]. Occasionally, the presence of an ovarian tumor is not recognized until the patient is examined just prior to or during labor and the birth canal is found to be obstructed by the mass[69]. Recommendations are that a gentle effort should be made to displace the mass upward. This frequently succeeds so that vaginal delivery is possible[67]. Aspiration has been discussed but because of the possibility of infection and particularly because of the chance of malignant intracystic transformation, this should not be undertaken. If it is impossible to displace the tumor, the patient should be treated by Cesarean section and abdominal removal of the ovarian cyst[69,70,71].

According to Hodgkinson[77], the capacity of the veins of the broad ligaments, chiefly the ovarian veins, increases 60 times by the 36th week of pregnancy and the venous pressure in these structures is doubled. Under the strain of muscular activity during labor or as a result of too vigorous manipulation before or during the third stage of delivery, one of these thin-walled dilated veins may rupture. Hodgkinson[78] collected 72 cases and added 3 new ones. The hemorrhage may be intraperitoneal, extraperitoneal, or both. Conger[31] reported one case that occurred immediately following delivery. The clinical picture is that of acute severe pain followed almost immediately by the picture of acute abdominal catastrophe. Ruptures have occurred from the 10th week of gestation to the 21st day following parturition and usually follow undue exertion on the part of either the patient or the attending physician. The obvious treatment is that of stabilization of the patient's general condition and immediate laparotomy with appropriate measures to stop the bleeding. Hodgkinson[78] points out that this development may explain some of the hitherto unexplained in-

stances of maternal death from hemorrhage in the absence of external bleeding. Since it may occur before, during, or after labor, this diagnosis should be considered in the event of any non-obvious development of acute abdominal pain followed by shock. The mortality rate of the reported cases approaches 50% and this can be lowered by active consideration of this possibility in the future[78,118].

THE HEAD, NECK AND THORAX. The intracranial complications of pregnancy consist of hemorrhage and neoplasm. The occurrence of subarachnoid hemorrhage during pregnancy is infrequent[186]. The diagnosis of hemorrhage is often confused with toxemia even though the toxemia triad is absent[45]. The commonest cause of subarachnoid hemorrhage in the childbearing age is that of a ruptured intracranial aneurysm[50,55]. Usually, these are congenital in origin although they may occur from arteriosclerosis or mycotic infection. The lesion is a berry-like sacculation in the angle regions of arterial bifurcation at the circle of Willis. The accident may occur at any time during pregnancy. In a recent series of 32 instances, 56% developed before, 12% during and 31.5% following labor[186]. The onset is sudden, with the development of occipital headache that rapidly becomes generalized. It is associated with nausea, vomiting, numbness, vertigo, visual changes, nuchal rigidity, and hemiplegia or coma. Spinal fluid pressure is increased and the fluid is xanthochromic. This complication must be differentiated from brain tumor, meningitis, hypertensive cerebral accident, trauma, leukemia, hemophilia and toxemia of pregnancy[50,55,85,186]. The prognosis is poor. In Walton's[185] series, the maternal mortality was 40% while the fetal mortality approached 66.3%[32].

The treatment depends upon an accurate determination of the etiology of the hemorrhage and upon the stage of gestation. The policy of watchful waiting is advocated by Walton[186] and Johnson[85]. Contrariwise Feldman *et al.*[50] state: "It seems to us that sound physical and physiological principles dictate that the first consideration is to control intracranial bleeding." By use of cerebral angiography, they determine the location of the aneurysm. The competency of the communicating arteries is judged by occlusion of the common carotid artery for 15 minutes to observe the patient's tolerance to ligation. If this test is satisfactory, the common carotid is ligated[50]. If the rupture occurs early in pregnancy, the patient may be allowed to progress to vaginal delivery with regional anesthesia and low forceps[55,186]. In third-trimester ruptures, delivery should be conducted with the least exertion for the mother. Cesarean section is suggested with local or regional anesthesia, reduction of hypertension and avoidance of postoperative vomiting[50,85]. A carefully conducted labor and vaginal delivery may be attended by less exertion than a Cesarean section with its postoperative annoyances. Opinions concerning sterilization are divided. Walton[185] claims that restriction of activity is of no value and a normal life should be encouraged. He believes that an emphasis upon a life of caution leads to disabling psychiatric sequela.

Cushing is quoted as stating that "pregnancy appears to be a provocative element in bringing brain tumors to light." On the other hand, the expected headache and vomiting of pregnancy may serve to obscure the early diagnosis until the patient is nearly blind before the tumor is suspected[148]. While there is no evidence that pregnancy hastens growth, the high hormonal levels may increase vascularization with a resulting intra-tumor hemorrhagic phenomenon[98].

Electroencephalography during pregnancy will aid in diagnosis and decision as to therapy[148,151]. While benign lesions may be watched, increasing intracranial hemorrhage indicates operative intervention. When a malignant lesion is suspected, prompt operation should be considered seriously. Cesarean section is the delivery route of choice because labor increases intracranial pressure. Since emergency postmortem or antemortem section will occasionally save a child, it should be considered in the rapidly deteriorating case[22,148,151].

Pregnancy is not a cause of dental caries and tooth decay does not progress more rapidly during pregnancy. There is no real metabolic reason why gestation should cause increased caries. In the care of the teeth, general anesthesia should be avoided in the early and late months of pregnancy and prophylactic antibiotics should be used in the presence of infection. Abscesses should be cared for as if the patient were not pregnant[67,107,179,199]. About 40% of pregnant patients have gingivitis. This is characterized by hyperplasia of the gum epithelium with the resulting tendency to bleed. About 2% of pregnant patients form tumors of the gum. This growth resembles a cyanotic epulis and is prone to hemorrhage and necrosis[202]. The tumor may be excised or removed electrosurgically, but recurrence is common. Fortunately, following delivery, the masses recede as a rule[6,179,187,202]. Recurrent attacks of acute tonsillitis in the pregnant patient should be treated by interval surgery. The risk of surgery is better than the complications of nephritis, rheumatic fever, bacteremia and peritonsillar abscess[67,107]. Quinsy or a peritonsillar abscess should be drained when fluctuation is observed. After the inflammation has subsided, tonsillectomy should be considered. Obstetrical patients with this complication should be treated as if they were not pregnant[26,67,107].

Thyroid fullness is observed in 30 to 40% of pregnant women[167,191]. The clinical problems consist of hyperthyroidism, single or multiple thyroid nodules, and thyroid carcinoma. The quoted incidence of hyperthyroidism extends from 0.016% to 1.4%[35,173,191]. A discussion of hyperthyroidism concerns the effect upon pregnancy and upon the infant, the effect of pregnancy upon the hyperthyroidism, and the proper management. Pregnancy is affected, in that the abortion rate is higher but the incidence of antenatal death, toxemia, premature labor, and complications of labor remains the same[5,59,191]. Fetal anomalies do not increase except for cretinism from ill-administered medication. Hyperthyroidism, if treated properly, is not aggravated, but pregnancy does seem to start this condition, occasionally[35]. Formerly, it was held that hyperthyroidism should be treated as if the patient were not pregnant. Dailey[35] recommended preoperative iodine and surgery. In 21 instances, this policy resulted in 14 normal babies, 3 therapeutic abortions and 4 spontaneous abortions. Bell[197] treated such patients with Thiourylene and surgery with 7 fetal deaths and no maternal loss.

Recent reports indicate the adequacy of medical management. Williams[197] with a series of 15 medically treated patients, reported no abortions and no premature infants. Astwood[5] reported 19 similar cases with 22 pregnancies and 22 living children of which 3 were premature. The medical regimen is complicated by placental permeability to both iodine and the thiourea compounds[5,62,73,140,191]. Radioactive iodine should never be used because of the danger to the infant. The other antithyroid drugs in improper dosage produce goitre or cretinism, or both, and nursing mothers should abstain from

these drugs while suckling their babies[5,35,73,197].

The management of benign neoplastic lesions of the thyroid is an unsettled question. Ward[187] advocates removal of all discrete single nodules for study, while Crile[197] has estimated that 6,675 solitary and apparently benign adenomas of the thyroid must be removed in order to prevent one patient from dying of carcinoma of the thyroid[197]. Multinodular glands should be left untouched unless they are the source of symptoms or show the characteristics of malignancy. The management of toxic adenoma and carcinoma is settled. All agree that adequate surgery is indicated regardless of the pregnancy[167,191,197,199]. Frazier[59] stated years ago that in the presence of definite thyroid malignancy the threat to life must be challenged by immediate surgical intervention.

Carcinoma of the breast occurs 3 times per 10,000 pregnancies, to comprise 2.8% of all breast cancers[193,194,195]. During pregnancy, breast tumors are camouflaged by the normal mammary changes that surround the tumors and cause delayed detection of the growth by both patient and physician. Delay in suspicion and in action during pregnancy averages 2 months for the patient and one month for the physician[195]. The discovery of a dominant mass in the breast inevitably leads to decision between cyst, fibroadenoma and carcinoma. The suspected cyst may be aspirated. Following withdrawal of the fluid, careful examination for residual nodularity is mandatory. If fluid is not obtained, the mass should be excised widely for microscopic examination. All solid tumors of the breast should be treated in a similar fashion. Approximately, three-fourths of the patients who are operated upon for breast cancer during pregnancy have already developed axillary metastasis. White[195] found in an analysis of 1,413 cases, that the survival rate for 5 years with coincident carcinoma and pregnancy was 13.5%; 21% without metastasis and 6.7% with metastasis. This is to be contrasted with the 55 to 60% survival rate in the nonpregnant state. The consensus is that this poor prognosis is due not to the effect of pregnancy upon breast carcinoma but to the delay in action. The treatment of proven carcinoma of the breast is immediate radical mastectomy, the earlier in pregnancy the better and the earlier after the development of the disease still the better. Surgery should be delayed only in the event of imminent delivery and even then, termination of pregnancy by the induction of labor or by Cesarean section should be considered[192,193,194,195]. Therapeutic abortion is no longer a portion of the therapy for co-existent breast carcinoma[124,192,193,194,195]. Indeed, Adair[1] surmised a possible counter hormone to restrain both chorionic tissue and breast cancer. He suggested that therapeutic termination of pregnancy may stimulate rather than retard extension of the malignant disease. White[195] reported that of 68 patients who had spontaneous or induced abortion, only 12 survived 5 years. He concluded that no definite beneficial effect follows termination of the pregnancy. Westberg[192] stated: "Nothing has been found to bear out the opinion that induced abortion should improve the prognosis. It would thus seem that the pregnancy has no very great effect on the prognosis of breast cancer apart from the fact that the patient delays in consulting a doctor and the doctor is inclined to postpone surgery."[192]

The occurrence of pregnancy following a radical operation for breast cancer raises the question of therapeutic abortion. White[195] states that when the pregnancy is permitted to continue, the gross 5- and 10-year survival rate is

similar to that without this complication. Finn[54], in a review of 10 patients who became pregnant following mastectomy, reported 7 successful terminations, with 3 therapeutic abortions because of either metastasis or proximity to the breast operation. A time limit between the preceding operation and the pregnancy is not determined, but knowledge of the growth characteristics of breast cancer suggests that 3 years would be a safe period[124,195].

In consideration of disease within the chest complicated by pregnancy, infection and neoplasm of the lungs as well as congenital and acquired heart disease bear consideration. The management of pulmonary tuberculosis in the pregnant patient demands awareness of the changing concepts in phthisiology. According to Turner[184], in a small minority of patients, pregnancy causes deterioration; in a large minority pregnancy is beneficial, and in a majority it has no obvious influence on the course of the disease. The treatment of tuberculosis in the pregnant patient is medical in most instances, but the newer surgical procedures should not be withheld when indicated[160]. Chamberlain[27] states, "Neither streptomycin nor any other drug can be expected to replace sound judgment in selecting the right operation for a specific patient, to be done at the proper time under good anesthesia and by a competent surgeon." Foci of tuberculosis that are not controlled by pneumothorax, pneumolysis or thoracoplasty can now be removed by segmental resection, lobectomy and pneumonectomy[34,80,162]. Corner and Nesbitt[34] reviewed the subject, "Pregnancy and Pulmonary Resection" to find 5 instances of successful results and to report 6 additional lobectomies during pregnancy. These were followed by 2 abortions and 4 continuations of pregnancy to term. They conclude that pneumonectomy and lobectomy may be performed during pregnancy with safety to mother and infant if it is essential to the welfare of the mother. Holden[80] reported 5 pulmonary resections for tuberculosis with one postoperative abortion. He concluded that major collapse therapy or resectional surgery, when indicated should be offered to the pregnant just as to the nonpregnant tuberculous patient. Schaefer[161], in a review of 100 abortions because of tuberculosis, concluded that therapeutic abortion for the pregnant tuberculous patient did not improve the end result[184].

Cancer of the lung is rare in the childbearing age. According to Ochsner[132], less than 5% of all lung cancers occur in women and one-fourth of these are in young women. Delay in diagnosis is common and the only curative therapy is radical extirpation of the entire lung rather than segmental resection. It seems that the management of the pregnancy should be similar to that of pregnancy complicated by carcinoma of the breast.

Heart disease now ranks high as a cause of maternal mortality. The congenital abnormalities: coarctation of the aorta, persistent ductus arteriosus, and interseptal defects are rare but offer a challenge during the pregnant state. According to Mendelson[119], in a review of 78,000 pregnant patients, 3.7% presented organic heart disease, 90% of which was rheumatic in origin. Seventy-five per cent of these had mitral stenosis and of this group, 12% fell into the activity classes three and four. In these classes, therapeutic termination of pregnancy and sterilization seemed justified formerly, but today, such a policy is untenable, until a careful medical regimen is tried, and if this fails, surgery is considered. Brock[20] states that the double millstone of disability and sterility is more than many patients can carry. According to Miller[122], 25,000

American women under 30 years of age have some degree of aortic coarctation. Under the medical regimen, 10% of 80 pregnant women with coarctation of the aorta died during pregnancy or in the immediate postpartum period[145]. The deaths were due to rupture of the aorta, cardiovascular accidents, aortitis or cardiac failure. Tebow[177] reported 3 successful surgical repairs of aortic coactation during pregnancy. He concluded that the operation should be done early in the pregnancy and great care should be exercised to avoid prolonged anoxia for the growing fetus. On the other hand, Cleland[29] and Dixon[40] advocated medical management and delivery to be followed by operative care of the coarctation some months later[8]. In selected cases, operation should be considered despite the theoretic fear of fetal death from anoxia. While no reported instances of patent ductus ligation were discovered, 3 such operations have been done at the Hospital of the University of Pennsylvania with safety for both mother and infant.

In some instances of mitral stenosis, medical care cannot answer the needs of the patient. Then, either the pregnancy must be terminated or mitral valvotomy must be considered. Mendelson[119] reported 35 collected cases and added 5 additional instances of operation with 2 maternal deaths, 1 residual insufficiency and 33 excellent results as to both mother and infant. Glover[61] reported 5 personal operations with complete maternal success and one fetal loss by abortion 6 weeks later. Mitral valvotomy should be considered only at the point of choice between this operation and therapeutic termination of pregnancy. Then, it may be a lifesaving procedure to both the infant and the mother. The operation is best done in the first trimester before cardiac work increases since this permits the heart to heal prior to the time that the peak load is encountered[190]. Following the operation, the conduct of the pregnancy and labor should depend upon the patient's response but evidence is accumulating to indicate that a normal prenatal course and a normal vaginal delivery, in the absence of obstetric indications for operative delivery, is to be anticipated[20,33,61,119,190].

THE ABDOMINAL ORGANS. The literature is sparse regarding complications involving incisional, inguinal and femoral hernias in pregnancy. It seems logical that the gradual enlargement of the uterus would push the bowel away from the inguinal and femoral defects. Since most incisional hernias are in the lower abdomen, this principle should apply here, but occasionally the uterus will protrude into the hernial sac. Boys[19] collected 5 such cases and he reported another one who was treated by Cesarean section at term.

The incidence of diaphragmatic hernia increases during pregnancy[96,138,153]. The background probably is a congenital weakness at the hiatus[44]. During pregnancy, the prolonged spasmodic increase in intra-abdominal pressure weakens these areas. Voluntary efforts during labor increase the intra-abdominal pressure[121] and the patient may strangulate the hernia[39]. The persistence of nausea and vomiting after the 12th week of pregnancy, hematemesis, intractable heartburn after the 20th week, epigastric distress after eating which is relieved by vomiting and aggravation of symptoms when recumbent should raise the question of hiatal hernia. The condition can mimic cholecysitis, peptic ulcer, coronary artery disease and pancreatitis[39,44,96,138,175]. Diddle's[39] review of gravid women with diaphragmatic hernias reveals that in 54 cases, 34 responded to medical care, one had a therapeutic abortion, 7 had

emergency surgery during or after labor and 11 died in the ante-, intra- or postnatal periods. Known symptomatic diaphragmatic hernias should be repaired before pregnancy. Interruption of pregnancy may be considered when the symptoms increase during gestation in spite of adequate medical treatment[123]. The medical management consists of frequent small feedings, with no food before bed. Elevation of the head of the bed will relieve nocturnal distress[39, 96]. The delivery should be either by Cesarean section or by forceps to shorten the second stage[138]. During a trial of labor, the patient may incarcerate and strangulate a hiatal hernia which presents a forbidding morbidity and mortality that is quoted by Penman[138] as 54.8% and by Kushlan[96] as 53.1%.

The incidence of cholelithiasis has been estimated at 10% of the population of this country. The female to male ratio is 2.2 to 1[30,155]. Robertson[155] proposed that gallstones are formed during the time of life when sexual functions are most active. He claims that functional disturbances which alter the absorption and secretory mechanisms of the gallbladder are responsible for the stone formation. Gallbladder disease frequently follows pregnancy[102]. During gestation, hypercholesteremia is found in the latter months and biliary tract motility is impaired[67,143]. Since the symptoms of cholecystitis are pain, belching, flatulence, nausea and vomiting, the diagnosis is often confused with the usual complaints of pregnancy[30]. The treatment of acute cholecystitis in pregnancy is conservative usually. Hamlin[72] reported the treatment of 7 cases medically with success. If the patient does not respond, surgical measures are indicated. The greatest dangers are rupture and gangrene of the gallbladder. According to Wilson[199], obstruction with jaundice, repeated attacks of colic, gangrene and empyema must be managed as in the nongravid patient. The mortality in the nonpregnant patient is 1.1%. Childs[28] reported 4 cholecystectomies in pregnancy with 1 abortion[30].

The diagnosis of acute pancreatitis concomitant with pregnancy is made in direct relationship to the index of suspicion[25]. Nausea, vomiting and epigastric distress are common complaints in the first trimester of pregnancy. Sudden onset of these symptoms associated with epigastric tenderness should suggest acute pancreatitis. Serum amylase and urinary diastase studies will aid in the diagnosis[56,87,99]. Pancreatitis falls into two general categories: acute interstitial and hemorrhagic. The interstitial variety is less severe and is frequently associated with cholecystic disease[99]. The latter type is a fulminating process during which the pancreas is digested by its own enzymes. It occurs in any trimester of pregnancy and is not related to parity. The etiology is unknown but the theories include: a stone blocking the pancreatic duct, hyperplasia of duct lining with obstruction to flow and external pressure from tumors, nodes or a pregnant uterus. The patient may be hard struck, presenting the picture of profound shock with rapid deterioration. Medical treatment comprises supportive methods such as blood, electrolytes, plasma, analgesics and antibiotics. Pancreatic secretions are suppressed by the use of the newer autonomic drugs and gastric suction is used to reduce the quantity of pancreatic stimulating hormones. The chemical peritonitis will often respond to a Miller-Abbott tube and the semi-Fowler position. The problem of when and whether to operate is difficult[56,87,99]. In the nonpregnant state, Fogerson[56] reported 16 deaths following 17 operatons. During pregnancy and the puerperium, Langmade[99] re-

ported 38 operations with 8 deaths. An exploratory laparotomy is indicated if the diagnosis is uncertain. While there is no need to operate for acute interstitial pancreatitis, in hemorrhagic pancreatitis, if the patient does not respond to adequate medical care, drainage of the lesser omental bursa and cholecystostomy may turn the tide[56]. Surgery is warranted in the presence of increasing jaundice, a distended gallbladder, pancreatic pseudocysts and abscess. The poor surgical and the encouraging modern medical results have discouraged surgical intervention as the initial therapeutic effort[56,87,99].

The incidence of appendicitis in pregnancy varies from 0.10% to 2%[10,79,115,135,144]. Eighty per cent of the cases occur during the first 6 months of gestation. The basic problem of delay by patient and doctor is of paramount importance. The patient feels that her symptoms are a normal part of pregnancy. The physician is often reticent to complicate pregnancy by an operation, especially when the diagnosis is equivocal. During pregnancy, prompt diagnosis is difficult. The abdominal pain is attributed to round ligament stretching. The nausea, vomiting, and anorexia are associated with the normal pregnant state. The leukocytosis is considered to be physiological. The location of the pain may not correspond to McBurney's point. The lack of abdominal tone reduces guarding, and rebound is difficult to judge in the presence of uterine enlargement[144]. In spite of these facts, the alert physician should not be misled. It is known from roentgenological studies performed during pregnancy that as the uterus enlarges, the appendix is usually displaced upward. The appendix shifts from the iliac fossa to above the iliac crest at term. The long axis changes from a downward to a vertical position[10]. The leukocytosis of appendicitis is more marked with a shift to the left, and the sedimentation rate is higher than with normal pregnancy. The history of previous attacks is very important, since the recurrent episode is frequent in pregnancy[22,115]. The differential diagnosis in the first trimester includes ectopic pregnancy, corpus luteum cyst, salpingitis and abortion. During the middle trimester, urinary tract disease, intestinal obstruction, ileus, ulcers, and gallbladder disease must be considered. The third trimester features labor, abruptio placentae and toxemia to be differentiated from appendicitis[117].

It has been shown that the maternal and fetal morbidity and mortality rise with delay and peritonitis. Out of 45 cases, fetal loss was 11.1% when the disease was limited to the appendix and 35.2% when peritonitis was present[79]. In 6 cases of appendicitis in late pregnancy, there were 3 fetal deaths, 4 cases of maternal morbidity and 1 maternal death. The delay in these cases was over 20 hours. A collective series of 208 cases of acute appendicitis showed a maternal mortality of 5.8% (12 deaths)[135]. Before antibiotics, Jerlov[84] and McDonald[108] separately and respectively reported that the incidence of abortion with appendicitis was 13.8% and 11.4%; with abscess formation 55% and 66% and with peritonitis 63% and 72%. McDonald[108] reported the maternal mortality of 1.76% with appendicitis which rose to 23.5% with abscess formation and increased to 30% with peritonitis[84,108]. Delay in diagnosis and in surgery is detrimental to both fetus and mother. The prognosis depends upon the duration of the disease and the stage of gestation. Babler[9] said that, "The mortality of acute appendicitis complicating pregnancy is the mortality of delay." The morbidity, mortality and premature labor increase with approach of term[10]. The poor prognosis in the presence of

perforation and peritonitis, as seen in Parker's[135] report, is associated with the apparent slowness of localization. This is probably related to the upward displacement of the appendix, the interference of the uterus with omental reaction and the mobility of the gravid uterus[37,79]. Parker[135] found free fluid, pus and fibrinous adhesions in the abdomen instead of the usual "walling-off" process.

The treatment of acute appendicitis in the gravid patient is immediate operation. Because of the failure to "wall off" the delay that may be indicated in the nonpregnant state is not indicated during pregnancy. If the complication arises at or near term, some advocate either a Cesarean section[79,115,117] or Porro hysterectomy[67]. The general feeling, however, is that with antibiotics, intravenous fluids and intubation at our disposal, the pregnancy should not be molested[10,28,37,135,144,152,201]. In the clinic in which the index of suspicion is high, the incidence of laparotomy for appendicitis rises. The number of normal appendices removed will also be increased but this is a justified elevation to avoid the tragedy that may follow procrastination[22,28,115,149,167].

Ulcerative colitis during pregnancy is characterized by a sudden onset, bloody diarrhea, cramps, fever and weight loss. The patients are usually young and emotionally unstable. They are strongly dependent and the disease frequently starts with the loss of psychologic support: be it mother, father, siblings, husband, children or a friend[51,65,113]. Ulcerative colitis has been a reason for therapeutic abortion in the past. However, it is now apparent that women with this disease can sustain pregnancy, in fact many of them improve at this time. Bargen[13] observed that 53% of his patients were better following delivery and 58% of Felsens'[51] series improved during pregnancy. He felt that in 70% of his patients with ulcerative colitis there was no indication for abortion. Contrariwise, Foster and Cohen's[58] review of the literature includes 170 cases in which they found 90 patients were improved or not affected, 80 were aggravated and 19 patients died. It was their opinion that the course of ulcerative colitis is usually marked by exacerbation of symptoms during pregnancy and that if colitis should develop during pregnancy severe adverse effects may be anticipated and a high mortality rate expected. Greene[65] observed that "The smoldering colonic cavity is often lighted by pregnancy." With the newer hormone preparations, ulcerative colitis during pregnancy should respond to a careful medical and psychologic regimen. Surgery is indicated only when an ileostomy becomes a life-saving procedure and it is to be preferred to abortion. Operation after pregnancy is indicated for polyposis and intractable chronic disease[113].

Neoplastic lesions of the lower bowel complicating pregnancy are uncommon. The average age of such patients is 32 years and the most common site is the descending colon. Loss of weight from the cancer is compensated by the weight gain in pregnancy. Secondary anemia is present and rectal bleeding is attributed to hemorrhoids. Abdominal cramps, nausea, vomiting and leukocytosis are frequent symptoms. Roentgenograms taken in the last 4 months are usually not dependable and tend to be misguiding[12,165,172,188]. The management of carcinoma of the bowel in pregnancy depends upon religious convictions of the parents, the stage of pregnancy, the desire for a child, the extent of the neoplasm and the presence or absence of complications such as obstruction, perforation or hemorrhage. Based on study of the literature, the following plan of management seems

logical. Lesions discovered in the first 20 weeks should be removed without interference with the pregnancy if possible. From the 20th to the 27th week, if the lesions seem resectable the pregnancy is sacrificed and the cancer treated. If the lesion is far advanced, the fetus is allowed to become viable and after a Cesarean section, a diversion operation is done for the cancer. After the 27th week, it is sensible to wait for a viable fetus which can be delivered by section, when the tumor operation will depend upon the individual problem at hand. In the face of complications, the patient's primary problem is treated without regard for the pregnancy. Delivery of a child vaginally is not a sound procedure if the lesion will be traumatized[12,46,114,165,188]. Banner[12] reviewed 41 cases in the literature with a maternal and fetal mortality of 63% and 50% respectively and added 7 cases with a fetal and maternal mortality of 14% each. Waters[188] reported an incidence of a perforated carcinoma of the cecum in the 34th week which was treated by surgical drainage and antibiotics. Later at term, low forceps delivery was followed in several weeks by an *en bloc* dissection. Three and one-half year follow-up showed that she is still clinically well. Pelvic delivery, after removal of the sigmoid colon and rectum, is uncomplicated if the pelvis is adequate[12,114,146].

The incidence of intestinal obstruction in pregnancy is reported from 0.0014% to 0.0034%[11]. The most frequent causative findings are adhesions, external hernias, pedunculated tumors, volvulus, pregnancy ileus or uterine pressure[11,189]. The presence of abdominal scars or the history of pelvic inflammatory disease should raise the index of suspicion. The diagnosis of intestinal obstruction during pregnancy is not made more frequently because it is not considered. Many obstructions occur in the large bowel. The two most common sites of bowel obstruction are the cul-de-sac and the right iliac fossa[189]. This complication is frequent in the multiparous patient with a relaxed abdominal wall. The onset is usually in the third trimester near term[92]. In the pregnant female, many of the symptoms and signs of intestinal obstruction are distorted by a gravid uterus. A frequent error is to mistake the colicky pain of obstruction for the initiation of labor[83]. If two enemas show no return, bowel obstruction must be considered. Roentgenograms should be taken for fluid and gas levels[11]. When the diagnosis is made, the patient must be prepared for operation by transgastric intestinal decompression, intravenous fluids, and restoration of the electrolytic balance and blood component values[189]. The surgical difficulties are compounded by the late diagnosis and the gravid uterus. The pregnancy should be ignored except when at or near term, when a Cesarean section should precede the intestinal surgery[11]. The presence of gangrene indicates immediate resection or exteriorization of the gangrenous loop[53]. When possible, the bowel should be decompressed by a proximal vent enterostomy or colostomy for the remainder of the pregnancy and the definitive bowel operation undertaken following the delivery[133].

The pelvic kidney, located partly or entirely below the pelvic brim, is a congenital abnormality. Short ureters and vessels are present and both organs may be fused to form a horseshoe kidney. The frequent association of an ectopic kidney with a short vagina and cervix was noted by Krahulik[93], and this usually applies to all congenital genital aberrations. The diagnosis of an ectopic kidney is made during the investigation of dysuria, hematuria and pyuria. Thirty-two and nine tenths per

cent of the patients have recurrent episodes of pain caused by poor drainage. The incidence and severity of hydronephrosis and pyelonephritis increases during pregnancy. When kidney disease is severe in early pregnancy, nephrectomy has been performed[2]. The pelvic kidney is a cause of dystocia. Potential damage to kidney tissue is definite and dangerous[2,93]. The latest recommendation in management of this complication is delivery by Cesarean section[93]. On the other hand, Anderson[2] studied 98 reports and added 14 new ones, with a maternal mortality of 10% and 0% respectively and a fetal loss of 30% and 37% respectively. He concluded that carefully attended vaginal delivery is safe in the majority of instances. He also warned against the removal of unidentified pelvic tumors at the time of Cesarean section. Several patients have died when this tumor happened to be the only kidney[2].

Renal calculi have a tendency to be propagated by stasis and infection. These factors are present in the pregnant patient but the incidence of calculi is not markedly elevated[4]. The stasis is increased by uterine pressure and the physiologic decrease in peristaltic activity. Other normal changes are dilatation of the renal pelvis and ureters with elongation of the ureters. This elongation will, in some patients, produce a "kink"[131]. Kidney or ureteral calculi pose both diagnostic and therapeutic problems in the gravid female[57, 95]. The symptoms consist of pain, dysuria, ureteral colic, polyuria, nausea, vomiting and macroscopic or microscopic hematuria. The diagnosis is abetted by radiologic evidence. Delay in kidney disease is dangerous. The therapeutic management emphasizes the value of renal tissue. When necessary, the kidney should be spared at the sacrifice of the fetus[170]. The basic policy is conservatism. Obstruction and infection must be curtailed to prevent functional loss. Cystoscopic examination and manipulation are routine on all patients except in the last trimester when this procedure is hazardous. Elective procedures should be done only in the third or fourth month when the surgery is either definitive, as nephrectomy or lithotomy, or some diversion procedure. In the last half of pregnancy, only emergency surgery is done. The indications for operation in a gravid female are increased loss of kidney function, severe pain from calculi and poor response of infection to conservative management[4,88,95,131,170].

Rupture of the liver in pregnancy as the result of trauma is not frequently observed. The cause and effect are usually obvious. However, when rupture of the liver occurs spontaneously, the diagnosis is seldom made preoperatively. Howard[81] collected 14 reports with 6 survivors, all after operation.

Most of these were in multiparous women in the last trimester of pregnancy and 60% of them showed signs of toxemia. It was suggested that convulsions lead to subcapsular hemorrhage with resulting rupture causing severe epigastric pain and collapse. The diagnosis is difficult and the need of immediate laparotomy is obvious. The management of liver hemorrhage consists of packing, suturing, electrocoagulation and compression clamps. The prognosis is poor. Maternal mortality has been high but with the present-day armamentarium the outlook is much better and the last two reported cases have survived[81,94].

Rupture of the spleen may be traumatic, pathological or spontaneous. These involve either rupture of the pulp or capsule, or both. Its association with pregnancy is considered to be coincidental. King[89] reported 24 collected instances and one new case. The diagnosis following trauma is usually

self-evident. In spontaneous rupture, the greatest proportion of cases occurs in the last trimester when the diagnosis is confused with the more common pathologic problems of pregnancy. The diagnostic features are left shoulder pain, epigastric tenderness and pain with signs of internal hemorrhage. When the uterus is not tender or hard and the fetal heart sounds are present, the physician should concentrate his attention on other abdominal organs, including the spleen[15]. The maternal mortality is high, 60 to 70%, but this figure will substantially decrease with the availability of blood and earlier surgery[14,15,89,101,110].

MISCELLANEOUS: THE INTEGUMENT, BLOOD VESSELS, BLOOD DYSCRASIAS. That the hormones of pregnancy affect the integument is evident by the mask of pregnancy, the darkening of the nipples and areola, and the linea nigra. A pigmented nevus also becomes darker and more prominent during pregnancy and the possibility of transformation of a benign nevus to a malignant melanoma, with its rapid growth dissemination and low curability rate, should be emphasized[134]. Pack[134] reported 32 malignant melanomata associated with pregnancy: 10 during pregnancy, 11 postpartum and 11 shortly before conception. The maternal mortality was 45% within 3 years with only 2-year follow-ups on 15 of the remaining patients. Two have survived 8 to 13 years respectively. Pigmented moles are not dangerous until puberty but after this, all suspected lesions should be excised. During pregnancy, surgical excision is recommended for nevi on the feet and the genitalia, nevi with increased pigmentation and those with ulceration, bleeding, pain and increased diameter or elevation. The excision should be wide and microscopic examination is mandatory. The treatment of malignant melanoma is wide, radical, surgical excision. The hormones of pregnancy apparently are responsible for the initiation of growth but not the maintenance of progression. Therefore, therapeutic abortion is too late to be of value[23,100,134]. Patients with the history of treated melanoma should not become pregnant for at least 5 years and sterilization may be justified[23,134].

Vascular disease during pregnancy is relatively common. The principally involved regions are those dependent areas of the body below the umbilicus, where increased venous pressure and pelvic congestion, promote vascular dilatation and stasis. Yet the occasional catastrophic vascular complication does occur, and of these the commonest is the rupture of an aneurysm. Most such aneurysms are congenital in origin, the three favorite locations of which are: the circle of Willis, the splenic artery and the aorta. The former has been considered in the section upon intracranial complications. In 27 collected instances of ruptured splenic aneurysms, Tonsykoski[183] pointed out the picture of acute upper-gastric pain followed by nausea, vomiting and almost immediate shock. He added one case to the group and stated that most patients did not survive because the diagnosis is not considered. Should the diagnosis be made, immediate splenectomy or ligation of the artery is imperative. Schnitker[164] collected 141 instances of dissecting aneurysm of the aorta under the age of 40. Forty-nine of these were female, of whom 24 were pregnant or shortly delivered. Rupture of an aortic aneurysm usually produces sudden severe substernal pain which radiates down both arms and to the back. Seventy-eight per cent of the group died from extension into the pericardial sac to produce cardiac tamponade. Tissue examination demonstrates a high incidence of congenital aortic narrowing with necrosis of the

media. The process seems to be that of weakening of the walls, the formation of a hematoma, then rupture. Sickel[168] collected 24 instances and added one. This patient died 5 days post-delivery from aortic rupture and cardiac tamponade. Advances in cardiovascular diagnosis and surgical therapy may soon permit adequate diagnosis and surgical care prior to the fetal termination that has been the story in the past.

In 1574, Ambrose Paré wrote that it is best not to meddle with varicose veins during pregnancy but this dictum may have outlived its validity. The modern surgical treatment of varicosities consists of either the injection of a sclerosing substance or ligation with stripping. Mullane[125] injected a sclerosing solution for 405 pregnant patients. Eighty-seven per cent of those who returned for check-up examination obtained satisfactory results while the remainder required postpartum operation. There were no complications following the injections. Of 414 patients treated by injection during pregnancy, Biegeleisen[16] reported 4% unsatisfactory results. There were no abortions, premature labors or emboli and no instances of phlebothrombosis or thrombophlebitis. Two series of 20 and 14 patients each were subjected to ligation and stripping by Peyton[141] and by Quattlebaum[147]. Both obtained excellent results with only one instance of postoperative phlebitis. The criteria of stripping are applied alike to pregnant and nonpregnant patients. The elimination of varicosities is a prophylactic measure against thromboembolic complications during pregnancy and should be considered in any phase of pregnancy[16,141]. Kimmel states, "the physician who has married a woman who has varicose veins of her dependent portions during pregnancy will automatically be converted"[158].

Many rectal diseases date their onset from pregnancy. While these conditions may regress following delivery, they usually persist to a minor degree, to become more severe with each succeeding gestation[106]. Known anorectal disease should be treated between pregnancies rather than deferred until the end of the childbearing period[106]. During pregnancy, hemorrhoids may become exceedingly painful or the source of considerable blood loss. Their surgical removal may be safely conducted between the 14th and 32nd week of gestation or in the immediate postpartum period[106].

Of the blood dyscrasias, congenital hemolytic anemia and idiopathic thrombocytopenic purpura are important. The former condition is rare and its association with pregnancy is more so. Two instances of splenectomy during pregnancy have been reported recently[14,149]. The risk of operation during pregnancy is considered to be less than the danger of the hemorrhagic complications without surgery during the ante-, intra-, and post-natal periods[14,110].

The diagnosis of purpura depends upon a decreased platelet count and prolonged bleeding following slight trauma. Bone marrow studies are interesting but noncontributory. Peterson[139] in review of the literature collected 66 pregnancies in 48 mothers with this disease. Splenectomy was done for 15 patients during pregnancy, with a fetal mortality of 31% and one maternal death. In the light of the newer developments in steroid therapy for this condition and based upon review of the literature, Peterson[139] suggests the following regimen in the management of idiopathic thrombocytopenic purpura during pregnancy: 1) Certain establishment of the idiopathic nature of the disease. 2) Whole blood transfusions to correct the anemia and multiple blood platelet transfusions. 3) Adequate steroid ther-

apy with emphasis upon cortisone and the corticotrophic substance. 4) Splenectomy if required by repeated relapses and only following adequate preparation and the medical production of remission. 5) Vaginal delivery unless obstetric indications require the abdominal route[139]. In regard to the infant, if the mother has a normal platelet count at the time of delivery, one-half of the children will be affected while three-quarters of those whose mothers have low count will be afflicted. The disease is self-limited in children, however, and persists for only approximately 2 months[139].

In this summary of the literature, the reviewers have attempted to include the conditions that are seen in obstetrical care which are or have been surgical in nature. Progress in the management of many of these conditions is due to the ever changing nature of modern medicine. Familiarity with these alterations is of basic importance to the attending physician and to the obstetric patient.

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SUMMARIO IN INTERLINGUA

(See page 654 for original article)

Tractamento de Angina de Pectore con Dinatric Acido Ethyleno-Diamino-Tetraacetic

1. Le tractamento de atheromatosis del arterias coronari, con su syndrome, communmente fatal, de angina de pectore, ha essite interprendite per medio del integration de cholesterol e calcium in le matrice.

2. Le agente chelante acido ethyleno-diamino-tetraacetic (AEDT) esseva usate a causa de su capacitate de remover calcium metastatic, specialmente ab le superficie endocardial del corde human.

3. Nos ha trovate que le action de AEDT disvitalisa calcium metastatic in texitos vivente, e que illo continua a influer super le economia del corpore longemente post le cessation del therapia.

4. Inter 20 patientes studiate, in qui angina de pectore esseva tractate con AEDT, 19 patientes supervivente obteneva marcate alleviation del symptomas. In 6 patientes le electrocardiogrammas anormal reverteva sub le therapia a AEDT a configurationes normal. In 7 patientes il habeva fixate cambiamentos de vetere infarcimentos myocardiac.

5. Patientes con angina de pectore causate per sclerosis medical del arterias coronari pote non esser afficite per AEDT.

6. In le patientes examinate le stabilitate del sero pathologic reverteva verso le norma.

7. Es discutite le datos supportante le hypothese de un relation intime inter calcium e cholesterol in le matrice atheromatose.

BOOK REVIEWS AND NOTICES

SUICIDE IN LONDON. AN ECOLOGICAL STUDY. Maudsley Monograph Series. By PETER SAINSBURY, B.A., M.D. CANTAB., D.P.M., Research Assistant, Institute of Psychiatry, University of London. Pp. 116; 6 ills. London: Chapman & Hall, Ltd., 1955 (Basic Books, Inc., New York, U.S. Agents). Price, $2.25.

THIS monograph represents a valuable contribution to our knowledge of the epidemiology of suicide. The present study is a sociological approach based on an examination of the differences in suicide rate in various neighborhoods and social groups in London and interpreting these in terms of their social and cultural structure. Such a study provides facts regarding the social conditions that play a role in suicide and therefore is useful in formulating a practical preventive approach. Among the significant observations are that suicide is over-represented in the higher socio-economic class, in those of higher occupational status, in sudden loss of ability to maintain a standard of living, in those living alone under various conditions of social isolation and in unstable mobile groups, in emigrees and above all in those with mental illness. R. K.

EXPERIMENTAL TUBERCULOSIS BACILLUS AND HOST. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.CH., AND MARGARET P. CAMERON, M.A., A.B.L.S., assisted by CECILIA M. O'CONNOR, B.Sc. Pp. 396; 66 ills. Boston: Little, Brown and Company, 1955. Price, $9.00.

No infectious disease has been subject to a more vast and varied research than has tuberculosis. Indeed, many of our fundamental ideas on allergy, immunity, host and parasite stem directly from tuberculosis research. In spite of the almost immeasurable amount of scientific work, and also despite the gratifying improvement in the clinical and public health aspects, there still remain large gaps in fundamental knowledge of the disease.

This volume includes the papers presented and discussions recorded October 5 to 7, 1954, in a Symposium on "The Tubercle Bacillus and the Reactions of the Host Tissues" under the auspices of the Ciba Foundation. Arnold R. Rich was Chairman; leading English, Continental and American scientists participated. Subjects discussed include: Various fractions of the tubercle bacillus and the reactions they produce; serological studies; tissue cultures; electron microscopy; hypersensitivity; desensitization; immunity; the action of cortisone; changes in human lung tissue reactions possibly related to chemotherapy; drug-resistant mutants of the tubercle bacillus. A short addendum on Experimental Leprosy calls attention to the many similarities and the important differences between the two mycobacterial infections.

Many of the papers are highly technical and may prove difficult for the average medical reader. The discussions, during which some two score leading research scientists freely "bat ideas around," are revealing and fascinating.

Typography is good, illustrations are well reproduced, index is adequate.

Serious students of tuberculosis will find this a most rewarding book. R. C.

JAMES PARKINSON (1755–1824). Edited by MACDONALD CRITCHLEY with the collaboration of WILLIAM H. MCMENEMEY, FRANCIS M. R. WALSHE AND J. GODWIN GREENFIELD. Pp. 268; 8 figs. on 2 plates. London: Macmillan & Co.; and New York: St. Martin's Press, 1955. Price, $4.50.

THE rarity of Parkinson's small Essay on the Shaking Palsy (1817) suggested to the guarantors of *Brain*, (who have sponsored this book) that the bicentenary of Parkinson's birth in 1755 might well be celebrated by a reprinting of his text, supported by a few essays on related aspects. Thus, in addition to a valuable summarizing Introduction by the Editor, we find a Biographical Essay by W. H. McMenemey, M.D., a careful and up-to-date discussion of the Pathology of Parkinson's Disease by J. Godwin Greenfield, M.D., and a Clinical Analysis of the Paralysis Agitans Syndrome by Sir Francis Walshe.

Since Parkinson's essay, not a great deal has been added to our knowledge of the essential etiology and lesions, the disordered function, and clinical manifestations of this baffling disease, even making due allowances for the expanded activities permitted by medical progress in the present century. Of course, the new information gained in all these directions, carefully portrayed and weighed in the present volume, are helpful in the solution of many of the unanswered questions. Negatively, too, we know more about what isn't

so in Parkinson's Disease. Osler today, for instance, would not say, as in 1906, that the cause would doubtless be found in the cerebral cortex. The discussion of post-infectious Parkinsonism and its relation to the idiopathic variety is of both practical and theoretical interest. Even the paragraph on terminology and the occasional usefulness of eponyms (p. xi) was stimulating to the reviewer's interest.

In the Biographical Essay, which occupies more than half of this book, Dr. McMenemey presents Parkinson's many sided life in considerable detail. Born in Shoreditch, where he spent his entire life, he became an apothecary and surgeon, like his father, John, to whom he had been apprenticed. Already in 1780 he had published material on physiology "of first quality," to be followed at irregular intervals by observations on the effects of fatal lightning strokes, resuscitation from drowning, hydrophobia, cancer, better trusses for rupture, the nature and cure of gout, and so on all with vivid clinical descriptions (several followed by necropsies that he and his son performed) and discussion of causes, this aspect weak to be sure but above the average that the limited knowledge of the times permitted. His clear post mortem description of a perforated appendix with general peritonitis is said to be the first recorded instance of appendicitis in the British literature. Medical writing, however, was not the only outlet for his industrious pen: ardent for social and parliamentary reform, he published anti-governmental pamphlets and books, some under his own name, but more anonymously or under the pseudonym of Old Hubert. A quite modern note was sounded when Parkinson, called before the Privy Council, at first declined to take the oath, "fearing it would seem to incriminate himself." Though he did not stop attacking the government even after the execution of Louis 16th, he avoided trial and imprisonment. He continued combining his favorite geological and fossil studies with professional practice and publication of observations. The last of these appeared in 1824, the year before his death. His one great work on the Shaking Palsy, appeared when he was 62. The name, Parkinson's Disease, first used by Charcot, is still preferred to Shaking Palsy or to Parkinson's Latin translation, Paralysis Agitans, neither including the essential element of rigidity. Notices of his death and even the encyclopedias speak of him briefly as a paleontologist and surgeon, without mentioning the Essay which has brought him medical immortality. Let us hope that the book here reviewed will help to rectify this omission, as well as producing the present views and observations on Parkinsonism that have practical value for the professional. E. K.

Farmacologia, Materia Medica Y Terapeutica. Volume I. By Luis E. Camponovo and Alfredo J. Bandoni. Pp. 644. Buenos Aires: Lopez & Etchegoyen, 1955.

This is an elementary textbook in pharmacology, materia medica and therapeutics. The first section of approximately 140 pages deals wih general pharmacology but in a more limited sense than the average English text for medical students. The second section of approximately 200 pages deals with prescription writing, posology, incompatibilities and pharmaceutical types of preparations. The rest of the book is devoted to the treatment of individual diseases. There are considered the antiparasitic drugs, the treatment of protozoal disorders, internal and external parasites. The treatment of other conditions is presumably to be covered in a future volume or volumes. The presentation is concise and clear and reflects the teaching experience of the authors. R. K.

Einführung in die Begutachtung innerer Krankheiten. By Johannes Brinkmann, M.D., and Heinrich Bornemann, M.D. Pp. 204. Leipzig: Georg Thieme Verlag, 1955. Price, DM 10.

This little volume is filled with excellent practical information on the evaluation of internal disease from the standpoint of compensation and related insurance problems, particularly as they occur in a country with long emphasis on socialized medical practice. All internists who read German will find here much of practical value. The book deserves to be translated into English. R. K.

Diseases of the Liver. Edited by Leon Schiff, M.D., Ph.D., Professor of Clinical Medicine, University of Cincinnati College of Medicine. Pp. 738; 244 ills. Philadelphia: J. B. Lippincott Co., 1956. Price, $16.00.

Doctor Schiff and his 27 collaborators have produced a very acceptable and practical text on the Diseases of the Liver. The contributors are all recognized authorities in their respective fields. Good editing has achieved proper balance and adequate coverage without undue duplication. The illustrations are numerous and well done and the format is convenient and agreeable. This text should find a wide appeal. R. K.

CHRISTOPHER'S TEXTBOOK OF SURGERY. Edited by LOYAL DAVIS, M.D., Chairman, Department of Surgery, Northwestern University Medical School. 6th ed. Pp. 1446; 1359 ills. Philadelphia: W. B. Saunders Company, 1956. Price, $15.50.

THIS new edition of a standard surgical textbook is edited by Dr. Loyal Davis and written by a number of well-known contributors. The double-column page is used throughout the book, and the illustrations and printing are excellent. There appear to be few typographical errors.

The section on the "History of Surgery" by Dr. Allen O. Whipple, and those on the "Physiology of Wound Healing" and "Surgical Bacteriology" by Drs. Altemeier, Stevenson and Meleney are outstanding. Certain sections of this book would benefit by more sub-headings and better organization, particularly from the point of view of the third and fourth year student.

The reviewer feels that the book can be recommended to anyone interested in the field of general surgery. Its use for third year medical students should include a well organized, fundamental outline in surgery. We think that it is well suited for the use of fourth year medical students. H. C.

NEW BOOKS

A Modern Pilgrim's Progress for Diabetics. BY GARFIELD G. DUNCAN, M.D., Clinical Professor of Medicine, Jefferson Medical College. Pp. 222. Philadelphia: W. B. Saunders Company, 1956. Price, $2.50.

A CLEAR insight into the manifold problems encountered in the treatment of diabetes is presented in a unique and attractive fashion in this small volume. The central figure is a young diabetic patient who obtains a position as a worker in a diabetic clinic. Her personal experiences and observations of diabetics in the home, clinic, hospital and in camps are depicted with descriptions of virtually all of the complications, acute and chronic, which may beset these patients. Although the book is intended primarily for those who have diabetes, the practitioner treating the disease will be helped by the excellent presentation of management of virtually every aspect of the condition. An abbreviated diabetic manual with instructions for self-care forms a useful appendix to the work. C. S.

The Halogenated Aliphatic, Olefinic, Cyclic, Aromatic, and Aliphatic-Aromatic Hydrocarbons Including the Halogenated Insecticides, Their Toxicity and Potential Dangers. BY W. F. VON OETTINGEN, M.D., PH.D., National Institute of Arthritis and Metabolic Diseases, National Institutes of Health. Pp. 430; 7 ills. Washington: U.S. Department of Health, Education and Welfare, 1955. Price, $2.50.

THIS book is concerned with the halogenated, olefinic, cyclic, aromatic, and aliphatic-aromatic hydrocarbons, including DDT and a number of its derivatives. The chemistry, analytical procedures, potential uses, investigative toxicology, clinical toxicology, and the prophylaxis and treatment of such poisonings are discussed.

Industrial physicians, toxicologists, veterinarians and others, who deal with these chemicals or with persons and animals exposed to them, will find this an important reference volume. C. Z.

The Comparative Endocrinology of Vertebrates. Part II. The Hormonal Control of Water and Salt-Electrolyte Metabolism in Vertebrates. Memoirs of the Society for Endocrinology, No. 5. Edited by I. CHESTER JONES AND P. ECKSTEIN, University of Liverpool. Pp. 124; 18 ills. New York: Cambridge University Press, 1956. Price, $4.75.

THIS memoir is based on the proceedings of a symposium held in July, 1954. It consists of seven papers reporting the results of investigations on the control of water and salt electrolyte metabolism in different vertebrates with particular reference to the role played by endocrine factors in these mechanisms. B. C.

Borderland Problems Between Physical Chemistry and Physiology. Edited by Y. ASAMI, Professor of Electrical Engineering, and K. HIGASI, Professor of Physical Chemistry, Hokkaido University. Pp. 130; 69 ills. Sapporo, Japan: The Research Institute of Applied Electricity, 1955.

THIS monograph consists of seven articles which are based on papers presented at a Symposium on Biological Science held at the Research Institute of Applied Electricity, Hokkaido University, Japan, in July, 1955. The first three papers are primarily concerned with problems in physical chemistry. The remaining articles, however, will be of interest to medical scientists: there are two papers (written in German) on the oxygen pressure in blood and on the gas exchange in the lung; an interesting report on certain aspects of the biological effects of ionizing radiations; and, finally, a consideration of electrophysiological problems of induced sleep. C. Z.

Röntgenaufnahmetechnik in der Hals-Nasen-Ohren-Heilkunde. BY DR. MED. BURKHARD SCHLOSSHAUER. Pp. 48; 72 ills. Stuttgart: Georg Thieme Verlag, 1956 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $2.85.

THE purpose of this monograph is to teach technicians the Roentgen-ray technique in the

field of otolaryngology. At first the machines and tables are described with special reference to the Schoenander table. In the following chapters the positioning of the patient for all standard views is shown with special reference to the paranasal sinuses, petrous bones, mastoid processes, mandible and upper cervical spine. Another chapter is written on the technique of sialography.

The illustrations in the book are excellent and instructive. As most of the technicians are not quite familiar with these special techniques, the book can be recommended very highly. W. B.

NEW EDITIONS

Starling's Principles of Human Physiology. Edited by Sir Charles Lovatt Evans, D.Sc., F.R.C.P., F.R.S., LL.D., Emeritus Professor of Physiology, University of London. 12th ed. Pp. 1233; 721 ills. some in color. Philadelphia: Lea & Febiger, 1956. Price, $12.50.

The high standards of previous editions are maintained. Special senses have been revised and improved by Dr. H. Hartridge. There are forty-one new figures. The presentation is still remarkable for its clarity and ability to get down to truly basic considerations. The book can be recommended with confidence. M. O.

Programs on Alcoholism Research, Treatment and Rehabilitation in the United States and Canada. A survey of progressive developments in the field of public action on alcoholism. 3rd ed. Pp. 36. New York: Licensed Beverage Industries, Inc., 1956.

This pamphlet contains the results of a survey conducted to determine what action was being taken by the various States in the U.S., and in the Provinces of Canada in the field of alcoholism research, treatment and rehabilitation in 1955. It is intended, the authors say, as both a handbook of information and a guide for action that could be undertaken in the future. O. E.

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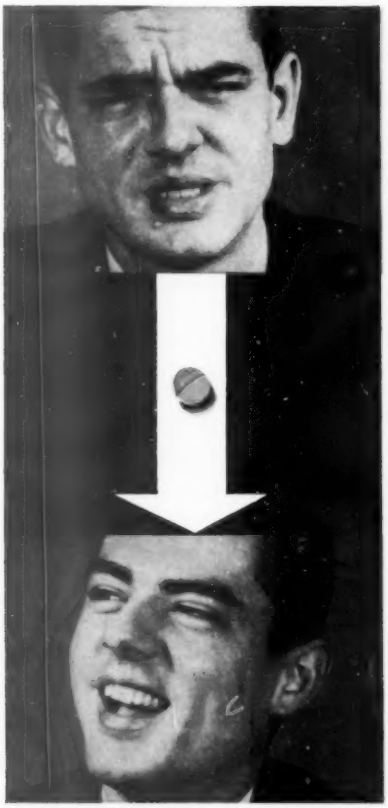

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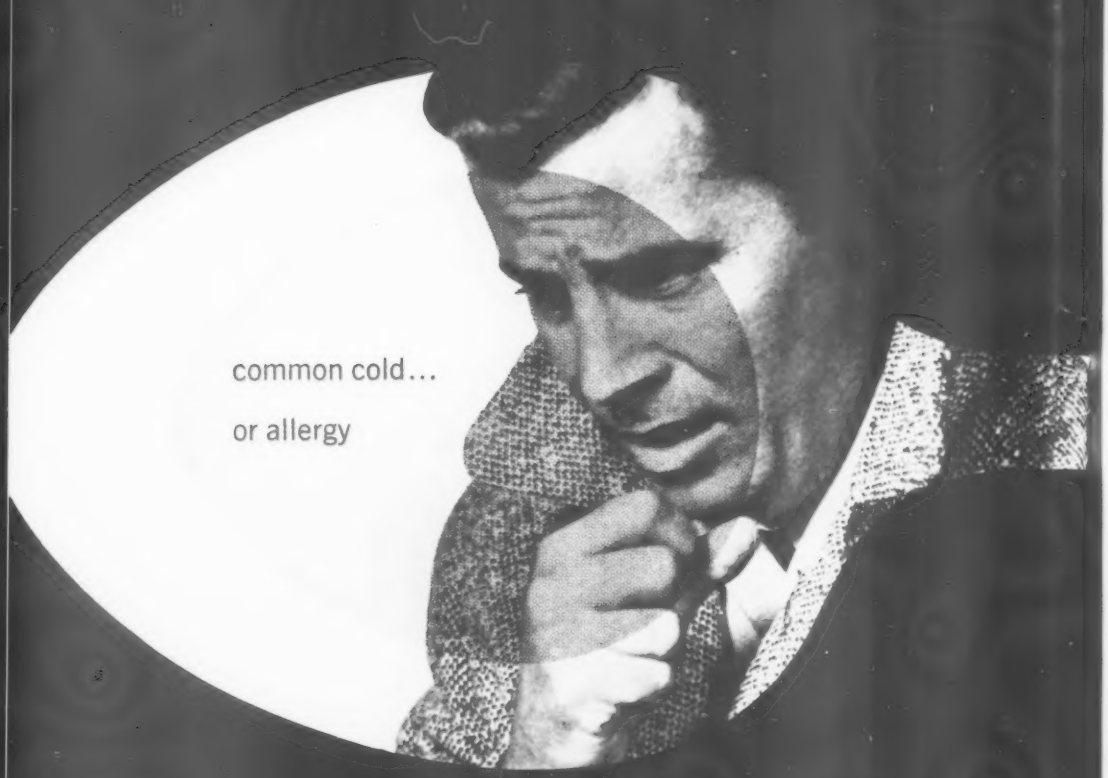

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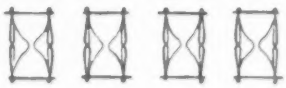
For the ambulant asthmatic: the only tablet that relieves asthma with nebulizer speed for 4 full hours 

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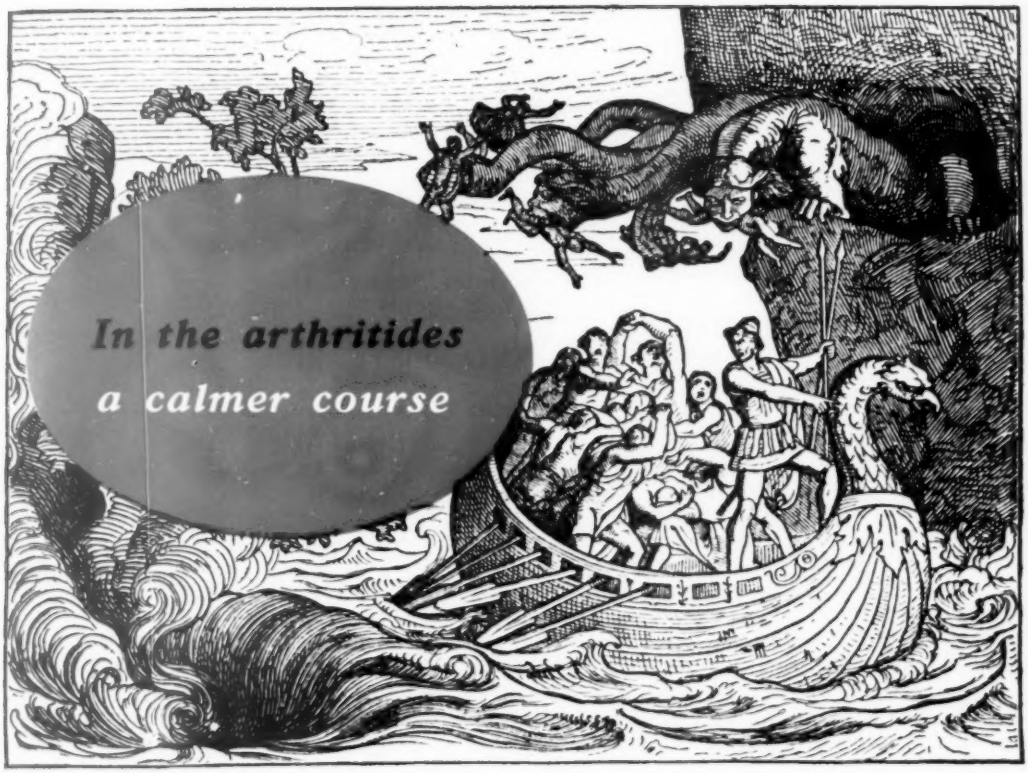

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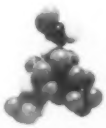

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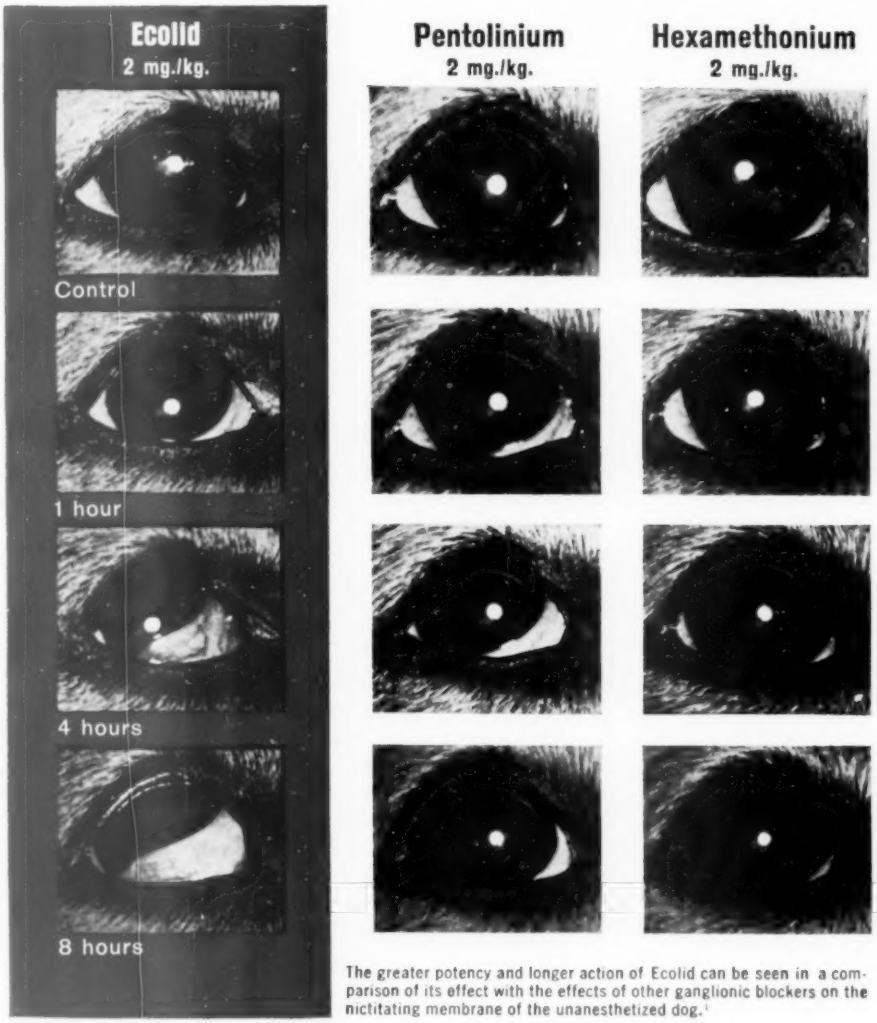

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1. Plummer, A. J., Trapold, J. H., Schneider, J. A., Maxwell, R. A., and Earl, A. E.: J. Pharmacol. & Exper. Therap. 115:172 (Oct.) 1955. 2. Grimson, K. S.: J.A.M.A. 158:359 (June 4) 1955. 3. Smith, J. R., and Hoobler, S. W.: Univ. Michigan M. Bull. 22:51 (Feb.) 1956. 4. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Circulation 11:733 (May) 1955.

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1. Kramer, P.: Med. Clin. North America, 39:1381, Sept. 1955.
2. Morrison, Samuel: Am. J. Gastroenterology 22:309 (1954).
3. Rossett, N. E., Rice, M. L., Jr., Gastroenterology 26:490 (1954).

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References: 1. Galambos, A.: Angiology 5:449 (Oct.) 1954; 2. Leake, C.D.: Ohio State M.J. 52:369 (April) 1956; 3. Moyer, J.H. et al.: A.M.A. Arch. Int. Med. 96:530 (Oct.) 1955.

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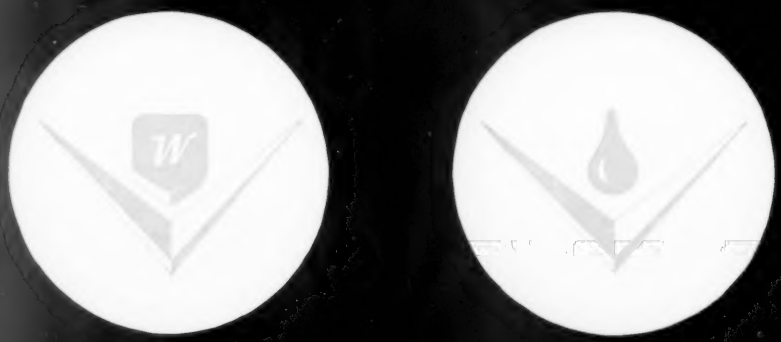

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1. Martin, W. J., et al.: J.A.M.A. *160*:925 (March 17) 1956.

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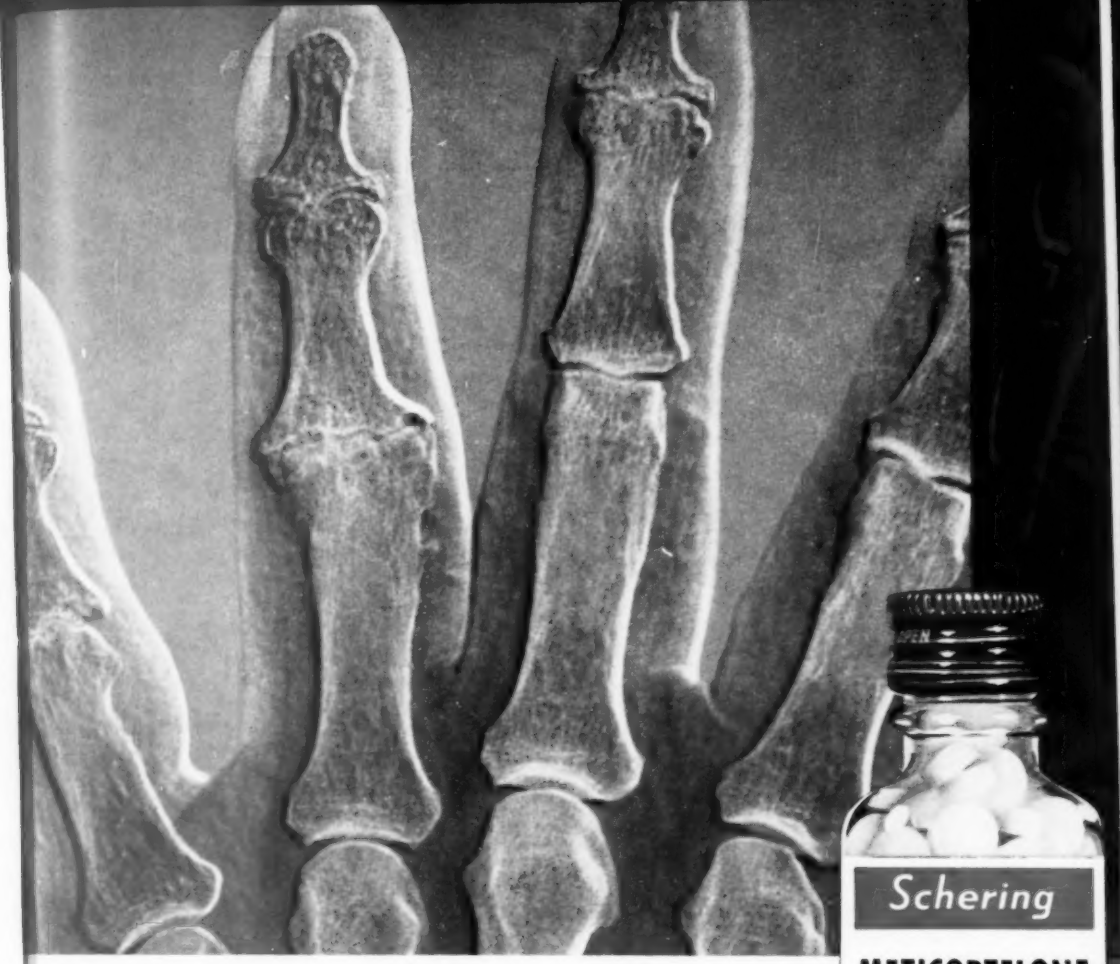

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Patient, white male, age 4, entered the clinic on 2/13/58, with a history of yellow discharge from the right ear, a fever, and sore throat of two days duration.

Temperature orally was 100°, pharynx infected, tonsils inflamed, crusted purulent material seen in right ear canal; tympanic membrane normal. Diagnosis -- tonsillitis and otitis externa.

Culture revealed Staphylococcus aureus, coagulase positive, resistant to penicillin and sensitive to erythromycin.

ERYTHROCIN (erythromycin) was started in doses of 25 mgm/kg -- 400 mgm in 4 equally divided doses.

After 24 hours of therapy, patient was afebrile and comfortable. T = 99.6. Throat slightly infected. Secretions in ear canal were dry and both tympanic membranes were normal.

Culture on 2/15 showed no coagulase positive staphylococci or other pathogens. On 2/22, follow-up exam showed him to be completely asymptomatic and free of unusual physical findings. The drug was stopped at this time.

Final Diagnosis: tonsillitis and otitis externa due to Staphylococcus aureus.

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1. Herrell, W. E., Erythromycin, Antibiotics Monographs, No. 1, p. 29, New York, Medical Encyclopedia, Inc., 1955.
Idem p. 30.

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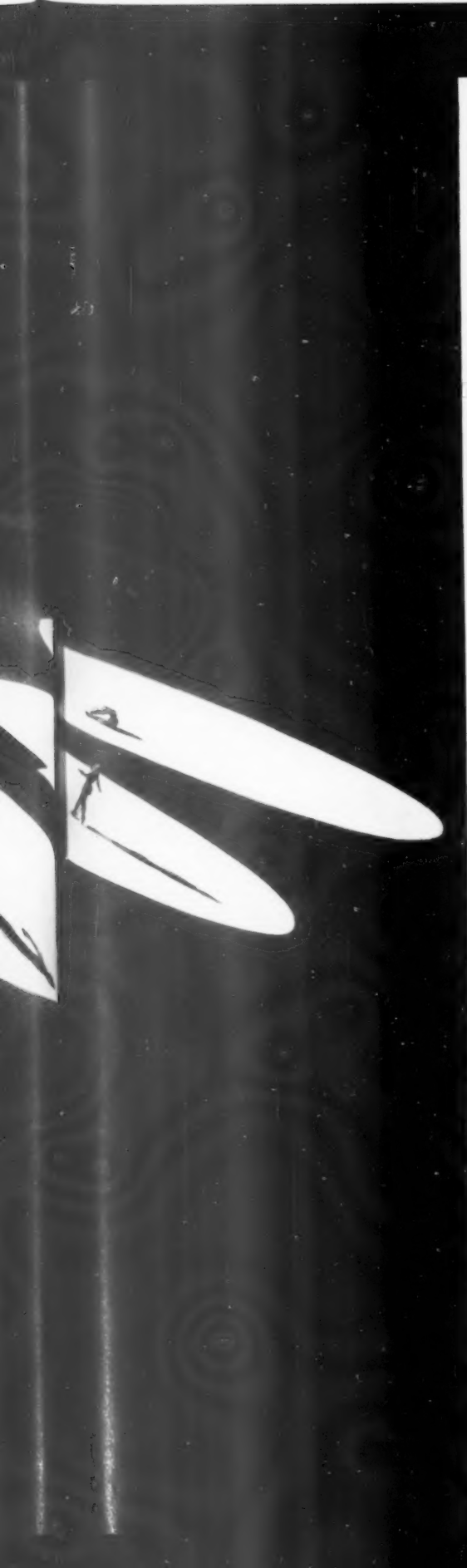

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1. Finland, M., *et al.*: *J.A.M.A.* 154:561 (Feb. 13) 1954.
2. Prigot, A. and Marmell, M.: *Antibiotics and Chemotherapy* 4:1117 (Oct.) 1954.
3. Trafton, H. and Lind, H.: *idem* 4:697 (June) 1954.
4. English, A., *et al.*: *idem* 4:411 (April) 1954.

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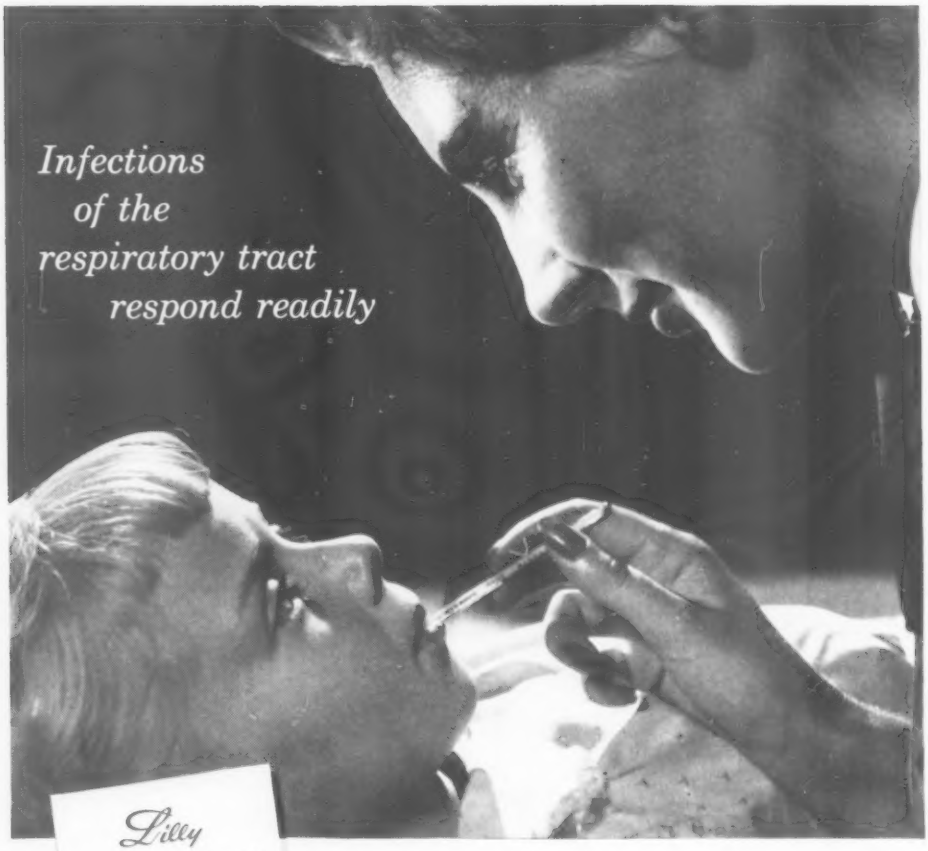

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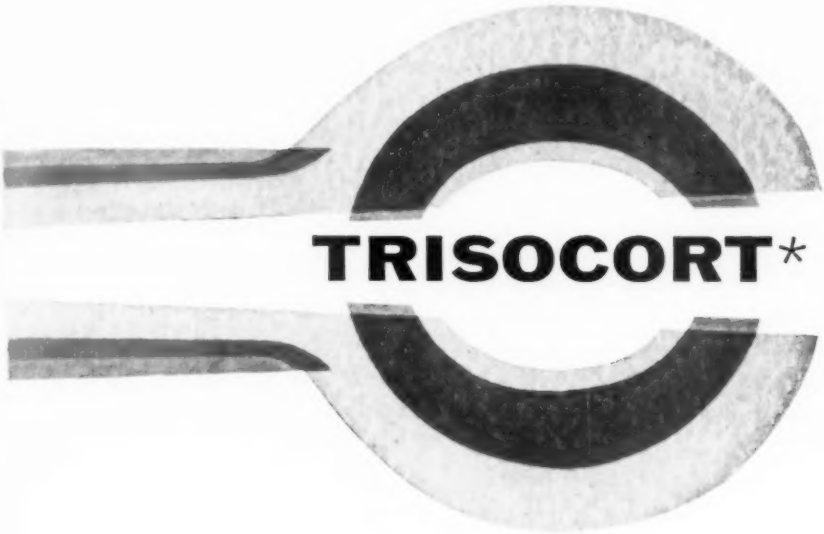

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Diagnosis and Treatment

By BEULAH CUSHMAN, M.S., M.D.

Attending Ophthalmologist, Passavant Memorial Hospital; Swedish Covenant Hospital; Women and Children's Hospital, Chicago, Illinois; Associate Professor of Ophthalmology, Northwestern University Medical School, Chicago

THIS sound work fills a long-felt need for a text to which post-graduate medical students in ophthalmology can refer for routine analysis of motor anomalies. It shows that by correction of strabismus through the extra-ocular muscles, which makes the eyes parallel, binocular single vision will result. The form in which the subject is presented has been developed entirely from the precepts as outlined by Dr. Alexander Duane in his monograph, and in the teachings and many papers of Dr. James Watson White.

FROM THE FORWORD BY DERRICK VAIL, M.D.

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The author is convinced that the visual field examination must not be conducted according to a rigid routine, and that ingenuity must be exercised to obtain the most information from the test. With this in mind, the section of this book devoted to the techniques of perimetry is couched in general terms as far as the actual conduct of the visual field examination is concerned. At the same time the student is supplied with the tools required to perform the examination and an account of their construction and the general principles underlying their use.

No methods or instruments for visual examination have been described unless the author has used them with personal satisfaction. Wherever possible, techniques have been simplified. While other publications cover limited parts of the field of ophthalmology, this text fills out the scotomatous patches. This presentation is that of a thoroughly grounded, broadly prepared, and experienced teacher of the subject. Just as quantitative methods increased the diagnostic value of perimetry, the original methods here presented offer additional help. The correlation of visual field interpretation with anatomy is of particular value.

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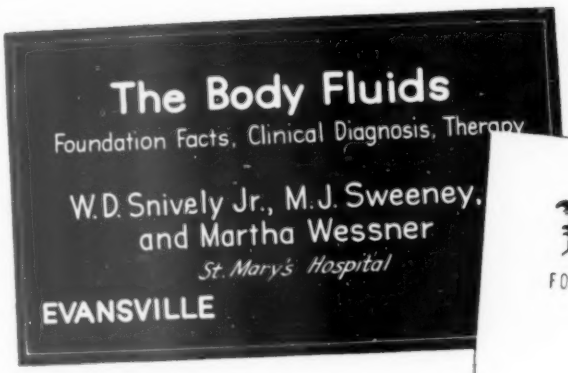
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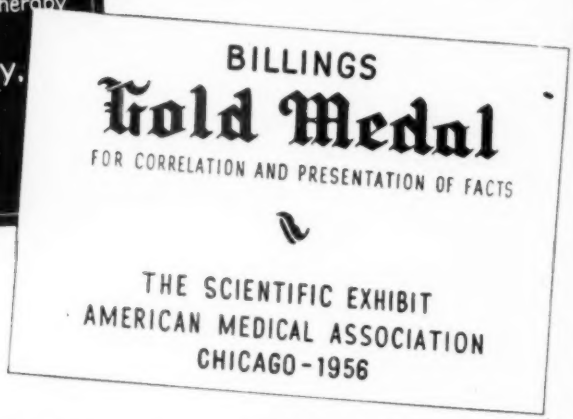

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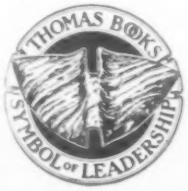

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References: **1.** Rosenberg, H. N., and Michelson, A. L.: Am. J. M. Sc. *230*:254 (Sept.) 1955. **2.** Kory, R. C., *et al.*: Am. Heart J. *50*:308 (Aug.) 1955. **3.** Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1953. **4.** Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952. **5.** Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

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1. Whitelaw, J.W.: Hypoparathyroidism in Children. *Bull. Vancouver Med. Assn.*, 30:116, Dec., 1953.
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3. Grollman, Arthur: Essentials of Endocrinology. Philadelphia, J. B. Lippincott Co., 2nd ed., 1947, p. 269.

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